From the Institute of Environmental Medicine
Karolinska Institutet, Stockholm, Sweden

Diet and risk of acute pancreatitis

Viktor Oskarsson

Karolinska Institutet

Stockholm 2016

Published by Karolinska Institutet
Printed by E-print AB 2016

ISBN 978-91-7676-241-7

Diet and risk of acute pancreatitis

Thesis for doctoral degree (Ph.D.)

by

Viktor Oskarsson

Principal Supervisor:
Professor Alicja Wolk
Karolinska Institutet
Institute of Environmental Medicine

Co-supervisors:
Associate professor Nicola Orsini
Karolinska Institutet
Department of Public Health Sciences

Associate professor Omid Sadr-Azodi
Karolinska Institutet
Institute of Environmental Medicine

Opponent:
Professor Jonas Manjer
Lund University
Department of Surgery

Examination Board:
Senior lecturer Michael Fored
Karolinska Institutet
Department of Medicine

Senior lecturer Mark Clements
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Associate professor Sara Regnér
Lund University
Department of Surgery

The Geirangerfjord, Norway

JAMA Intern Med. 2016;176(2):164. doi:10.1001/jamainternmed.2015.7069.

Courtesy of: Viktor Oskarsson, MD, Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

The Geirangerfjord, Norway

Poem

The shame of things to come

In a rusty diner in Tuskegee,
seven sins have reunited. Their abominations,
once seen in sober light, blurred and diminished
by the intoxication of ignorance. Our shame,
of all that followed in the steps of the Kristallnacht,
silent. As if the collective memory of a generation
dies with its last optic nerve.

On the wide-stretched shores of Europe,
seven hundred and seventy-seven Aylan Kurdis are buried. Their crimes,
the unthinkable thought of equality, judged and sentenced
by the show trial that is known as a political poll. Our horror,
of all that will follow in the steps of the again-lost humanity,
superficial. As if a modern day Normandy, where lead and hate
are the welcoming committee for defenceless fetuses,
is a tale of fiction.

Viktor Oskarsson MD

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

viktor.oskarsson@ki.se

doi: 10.5694/mja15.01283

Preface

You have in your hands my doctoral thesis, "Diet and risk of acute pancreatitis", which examines the association between diet and development, recurrence, and progression of acute inflammation in the pancreas (so-called acute pancreatitis) using data from a large group of Swedish men and women. (And to be more specific: the thesis focuses solely on the subtypes of acute pancreatitis that are not caused by gallstones.) It consists of 6 major chapters (Background; Aims; Material and methods; Results; Discussion; and Final remarks), with each of them being divided into a number of sections and subsections. The chapters can be read separately from each other, although the extent of which depends on the reader's experience of acute pancreatitis and/or epidemiology; but read together there is a logical flow to my arguments, starting from the hypothesis and ending with the conclusion.

To write this thesis has been one of the most, if not the most, exhaustive and time-consuming projects that I have ever undertaken. It has at the same time been an extremely rewarding project, giving me a greater understanding of epidemiology in general and of nutritional epidemiology in particular. I am also very pleased with the end result and feel confident that the thesis contains something of interest for researchers, health care providers, and laypeople; either something to like and agree with or something to dislike and disagree with.

Not only does this thesis sum up my 5 years of PhD-studies, it is also the final chapter of all of my studies here at Karolinska Institutet (which started nearly a decade ago, in 2006, when I was accepted to medical school). It has been a long and interesting ride. And I am proud that this is my last goodbye.

Viktor Oskarsson
Stockholm, Sweden
April 27, 2016

Abstract (English)

Acute pancreatitis is a sudden inflammation of the pancreas. It has a broad spectrum of clinical outcomes, ranging from mild and self-limiting to severe and potentially fatal, and is often followed by recurrent attacks and/or progression to a chronic disease state (so-called chronic pancreatitis); especially if it is classified as non-gallstone-related acute pancreatitis. Alcohol abuse is considered to be the most important risk factor for non-gallstone-related acute pancreatitis. Even though dietary factors also might be risk factors, the literature on the role of diet in the development, recurrence, and progression of non-gallstone-related acute pancreatitis is sparse.

A total of 5 studies were included in this thesis, for which the specific aims were to study: **(Paper I)** the association of fruit and vegetable consumption with incidence (first occurrence) of non-gallstone-related acute pancreatitis; **(Paper II)** the association between glycemic load (a measure that combines quantity and quality of carbohydrates) and incidence of non-gallstone-related acute pancreatitis; **(Paper III)** the association between fish consumption and incidence of non-gallstone-related acute pancreatitis; **(Paper IV)** the association between coffee drinking and incidence of non-gallstone-related acute pancreatitis; and **(Paper V)** the association between overall diet quality and risk of recurrent and progressive pancreatic disease after an incident episode of non-gallstone-related acute pancreatitis.

In the incidence studies **(Paper I–IV)**—which used data from a large group of Swedish men and women who had completed a food-frequency questionnaire in 1997 (study samples ranging from 71,458 to 81,100 persons), and who were followed up for a maximum of 12 to 15 years via linkage to national health registers—I observed that incidence of non-gallstone-related acute pancreatitis (study samples ranging from 320 to 383 cases) had an inverse association (lower risk) with consumption of vegetables **(Paper I)** and fish **(Paper III)**, a positive association (higher risk) with consumption of high-glycemic load foods **(Paper II)**, and a null association with consumption of fruit **(Paper I)** and coffee **(Paper IV)**. In the recurrence and progression study **(Paper V)**—which used data on the 386 persons who had been diagnosed with incident non-gallstone-related acute pancreatitis between 1998 and 2013, and who were subsequently followed up until the end of 2014 (mean follow-up of 4.8 years)—I observed no clear association between overall diet quality (calculated using a recommended food score, which was based on 25 healthy food items) and risk of recurrent and progressive pancreatic disease (defined as recurrent episodes of acute pancreatitis and/or incident episodes of chronic pancreatitis or pancreatic cancer; study sample of 90 cases).

Taken together, these findings suggest that diet, a previously overlooked factor, might be important in the primary prevention of non-gallstone-related acute pancreatitis—and as such, they uniquely contribute to the existing literature on the role of diet in health promotion and disease prevention. On the other hand, the findings are less supportive of an important role of diet in the secondary prevention of non-gallstone-related acute pancreatitis (ie, as a potential way to reduce recurrence and progression), at least for the overall diet quality; even though a role of individual food items and nutrients cannot be excluded.

Abstrakt (Svenska)

Akut pankreatit är en plötslig inflammation i bukspottkörteln. Den har ett brett spektrum av kliniska symptom, allt från lindriga och övergående till allvarliga och potentiellt livshotande, och följs ofta av återkommande attacker och/eller progression till ett kroniskt sjukdomstillstånd (så kallad kronisk pankreatit); särskilt om den klassificerats som icke gallstensrelaterad akut pankreatit. Alkoholmissbruk anses vara den främsta riskfaktorn för icke gallstensrelaterad akut pankreatit och även om kostfaktorer också kan påverka risken är den tillgängliga litteraturen om kostens roll i utvecklingen, återinsjuknandet och progressionen av icke gallstensrelaterad akut pankreatit begränsad.

Sammanlagt ingick fem studier i denna avhandling, där de specifika målen var att studera: **(Paper I)** sambandet mellan frukt- och grönsakskonsumtion och incidens (första förekomst) av icke gallstensrelaterad akut pankreatit; **(Paper II)** sambandet mellan glykemisk belastning (ett mått som kombinerar kvantitet och kvalitet av kolhydrater) och incidens av icke gallstensrelaterad akut pankreatit; **(Paper III)** sambandet mellan fiskkonsumtion och incidens av icke gallstensrelaterad akut pankreatit; **(Paper IV)** sambandet mellan kaffedrickande och incidens av icke gallstensrelaterad akut pankreatit; och **(Paper V)** sambandet mellan övergripande kostkvalitet och risk för återkommande och progressiv pankreassjukdom efter en förstagångsepisod av icke gallstensrelaterad akut pankreatit.

I incidensstudierna **(Paper I–IV)** – vilka använde data från en stor grupp svenska män och kvinnor som svarat på ett livsmedelsformulär under 1997 (total studiestorlek mellan 71 458 och 81 100 personer) och som sedan följdes upp via koppling till nationella hälsoregister (total uppföljningstid mellan 12 och 15 år) – observerade jag att incidens av icke gallstensrelaterad akut pankreatit (total fallstorlek mellan 320 och 383 fall) hade ett omvänt samband (lägre risk) med konsumtion av grönsaker **(Paper I)** och fisk **(Paper III)**, ett positivt samband (högre risk) med konsumtion av livsmedel med hög glykemisk belastning **(Paper II)** och inget samband med konsumtion av frukt **(Paper I)** och kaffe **(Paper IV)**. I återfalls- och progressionsstudien **(Paper V)** – vilken använde data på de 386 personer som diagnosticerats med en förstagångsepisod av icke gallstensrelaterad akut pankreatit mellan 1998 och 2013 och som sedan följdes upp via koppling till nationella hälsoregister till slutet av 2014 (genomsnittlig uppföljningstid på 4,8 år) – observerade jag inget tydligt samband mellan övergripande kostkvalitet (beräknad med ett så kallat ”recommended food score” vilket baserades på 25 hälsosamma livsmedel) och risk för återkommande och progressiv pankreassjukdom (definierad som återkommande episoder av akut pankreatit och/eller förstagångsepisoder av kronisk pankreatit eller pankreascancer; total fallstorlek på 90 fall).

Sammantaget tyder dessa resultat på att kosten, en tidigare förbisedd faktor, kan vara en viktig del i det primära förebyggandet av icke gallstensrelaterad akut pankreatit – och resultaten bidrar därmed på ett unikt sätt till den allmänna litteraturen om kostens betydelse för hälsa och sjukdom. Å andra sidan är resultaten mindre stödjande för att kosten har en viktig roll i det sekundära förebyggandet av icke gallstensrelaterad akut pankreatit (det vill säga de åtgärder som syftar till att minska återfall och/eller progression), åtminstone för den övergripande kostkvaliteten; även om ett samband med individuella kostfaktorer inte kan uteslutas.

List of publications included in the thesis

The thesis is based on 5 publications (listed below), which will be referred to in the text by their Roman numerals. Each publication is reproduced in full at the end of the thesis.

I. **Oskarsson, V.**, Sadr-Azodi, O., Orsini, N., Andrén-Sandberg, Å., & Wolk, A. (2013). Vegetables, fruit and risk of non-gallstone-related acute pancreatitis: A population-based prospective cohort study. *Gut*, *62*(8), 1187-1194.

II. **Oskarsson, V.**, Sadr-Azodi, O., Orsini, N., Andrén-Sandberg, Å., & Wolk, A. (2014). High dietary glycemic load increases the risk of non-gallstone-related acute pancreatitis: A prospective cohort study. *Clinical Gastroenterology and Hepatology*, *12*(4), 676-682.

III. **Oskarsson, V.**, Orsini, N., Sadr-Azodi, O., & Wolk, A. (2015). Fish consumption and risk of non-gallstone-related acute pancreatitis: A prospective cohort study. *American Journal of Clinical Nutrition*, *101*(1), 72-78.

IV. **Oskarsson, V.**, Sadr-Azodi, O., Orsini, N., & Wolk, A. (2016). A prospective cohort study on the association between coffee drinking and risk of non-gallstone-related acute pancreatitis. *British Journal of Nutrition*, *115*(10), 1830-1834.

V. **Oskarsson, V.**, Sadr-Azodi, O., Discacciati, A., Orsini, N., & Wolk, A. (2016). A prospective cohort study of overall diet quality and risk of recurrent and progressive pancreatic disease among individuals with non-gallstone-related acute pancreatitis. *Manuscript.*

List of publications not included in the thesis

Publications that were not included in the thesis, but published or submitted by me during my time as a PhD-student, are listed below.

- **Oskarsson, V.**, Mehrabi, M., Orsini, N., Hammarqvist, F., Segersvärd, R., Andrén-Sandberg, Å., & Sadr-Azodi, O. (2011). Validation of the harmless acute pancreatitis score in predicting nonsevere course of acute pancreatitis. *Pancreatology*, *11*(5), 464-468.
- **Oskarsson, V.**, Orsini, N., Sadr-Azodi, O., & Wolk, A. (2014). Postmenopausal hormone replacement therapy and risk of acute pancreatitis: A prospective cohort study. *CMAJ: Canadian Medical Association Journal*, *186*(5), 338-344.
- Razavi, D., Lindblad, M., Bexelius, T., **Oskarsson, V.**, Sadr-Azodi, O., & Ljung, R. (2016). Polypharmacy and risk of acute pancreatitis. *Submitted manuscript*.
- Nordenvall, C., **Oskarsson, V.**, & Wolk, A. (2015). Inverse association between coffee consumption and risk of cholecystectomy in women but not in men. *Clinical Gastroenterology and Hepatology*, *13*(6), 1096-1102.e1.
- Crippa, A., Discacciati, A., Orsini, N., & **Oskarsson, V.** (2016). Letter: Coffee consumption and gallstone disease - A cautionary note on the assignment of exposure values in dose-response meta-analyses. *Alimentary Pharmacology & Therapeutics*, *43*(1), 166-167.
- Nordenvall, C., **Oskarsson, V.**, Sadr-Azodi, O., Orsini, N., & Wolk, A. (2014). Postmenopausal hormone replacement therapy and risk of cholecystectomy: A prospective cohort study. *Scandinavian Journal of Gastroenterology*, *49*(1), 109-113.
- Nordenvall, C., **Oskarsson, V.**, & Wolk, A. (2016). Fruit and vegetable consumption and risk of cholecystectomy: A prospective cohort study of women and men. *Submitted manuscript*.
- Discacciati, A., **Oskarsson, V.**, & Orsini, N. (2015). STPHCOXRCS: Stata module to check proportional-hazards assumption using restricted cubic splines. [Statistical component in Stata]. *Boston College Archives*. Available from https://ideas.repec.org/c/boc/bocode/s458073.html

Contents

1 Background 1
1.1 The pancreas 1
1.2 Acute pancreatitis 2
1.2.1 Pathogenesis and pathophysiology 2
1.2.2 Clinical aspects 3
1.2.3 Descriptive epidemiology 5
1.2.4 Analytical epidemiology (risk factors) 8
1.3 Diet and health 10
1.3.1 Fruit and vegetables 10
1.3.2 Glycemic load 10
1.3.3 Fish 11
1.3.4 Coffee 11
1.3.5 Recommended food score 11
1.4 Diet and risk of acute pancreatitis 12
2 Aims 15
3 Material and methods 17
3.1 Study population 17
3.1.1 The Swedish Mammography Cohort and the Cohort of Swedish Men 17
3.1.2 National health registries 18
3.2 Exposure assessment 19
3.2.1 Fruit and vegetables (Paper I) 19
3.2.2 Glycemic load (Paper II) 19
3.2.3 Fish (Paper III) 20
3.2.4 Coffee (Paper IV) 20
3.2.5 Recommended food score (Paper V) 20
3.3 Covariate assessment 21
3.4 Outcome assessment 22
3.4.1 Non-gallstone-related acute pancreatitis (Paper I–IV) 22
3.4.2 Recurrent and progressive pancreatic disease (Paper V) 24
3.5 Analytical cohorts and follow-up periods 25
3.5.1 Incidence studies (Paper I–IV) 25
3.5.2 Recurrence and progression study (Paper V) 25
3.6 Statistical analyses 27
3.6.1 Cox regression 27
3.6.2 Statistical software 32
4 Results 33
4.1 Incidence studies (Paper I–IV) 33
4.1.1 Main results 33
4.1.2 Sensitivity analysis 36
4.1.3 Subgroup analysis 37
4.2 Recurrence and progression study (Paper V) 38
4.2.1 Main results 38
4.2.2 Sensitivity analysis 38
5 Discussion 41
5.1 Main findings 41
5.1.1 Incidence studies (Paper I–IV) 41
5.1.2 Recurrence and progression study (Paper V) 44
5.1.3 Potential biological mechanisms 46
5.2 Methodological considerations 49

5.2.1 Study design 49
5.2.2 Random error 51
5.2.3 Systematic error (bias) 52
5.2.4 Generalizability 58
6 Final remarks 59
6.1 Conclusion 59
6.2 Future research 60
7 Acknowledgements 61
8 References 63
9 Supplementary material 77
9.1 References used in Figure 1.3 77
9.2 References used in Figure 1.4 78
9.3 Table S.1 80

List of abbreviations

BMI	Body mass index
CCK	Cholecystokinin
CI	Confidence intervals
COSM	Cohort of Swedish Men
DAG	Directed acyclic graph
DALY	Disability-adjusted life-year
ERCP	Endoscopic retrograde cholangiopancreatography
FFQ	Food-frequency questionnaire
HR	Hazard ratios
ICD	International Classification of Diseases
LCn-3 PUFAs	Long-chain n-3 polyunsaturated fatty acids
MEsH	Medical subject headings
NOMESCO	Nordic Medico-Statistical Committee
NFκB	Nuclear factor kappa-light-chain-enhancer of B cells
PPV	Positive predictive value
RFS	Recommended food score
SD	Standard deviation
SMC	Swedish Mammography Cohort
SNPR	Swedish National Patient Register

1 Background

1.1 The pancreas

The pancreas, named after the Greek words *pan* (all) and *kreas* (flesh), is an abdominal glandular[1] organ that is located behind and below the stomach as well as in proximity to other organs, including the duodenum (part of the small intestine) and the gallbladder (Ansari, 2014) (Figure 1.1a). In healthy adults, the pancreas measures 15 to 20 cm in length and 75 to 100 g in weight and can be divided into 4 anatomical subsections: head, neck, body, and tail. The pancreatic duct, which goes diagonally from the tail down to the head, is joined in its terminal part by the common bile duct, whereafter they have a shared connection to the duodenum via the duodenal papilla.

The pancreas contains a mixture of exocrine and endocrine glandular tissue (Andersson, 2010; Ansari, 2014), and its physiological function is to regulate food digestion (exocrine part) and blood glucose concentrations (endocrine part). The exocrine part, which mainly consists of acinar cells, secretes inactive precursors of digestive enzymes (ie, protease, amylase, and lipase) via the pancreatic duct (Figure 1.1b). Once activated in the duodenum, they are responsible for further digestion of proteins, carbohydrates, and fats. The exocrine secretion is stimulated by the hormone cholecystokinin (CCK), which, in turn, has consumption of high-fat and high-protein meals as its main stimulus. The endocrine part, which is concentrated to shattered clusters of endocrine cells (so-called pancreatic islets), secretes hormones via surrounding blood vessels in response to changes in blood glucose concentrations (Figure 1.1b), most notably insulin (which decreases glucose concentrations) and glucagon (which increases glucose concentrations).

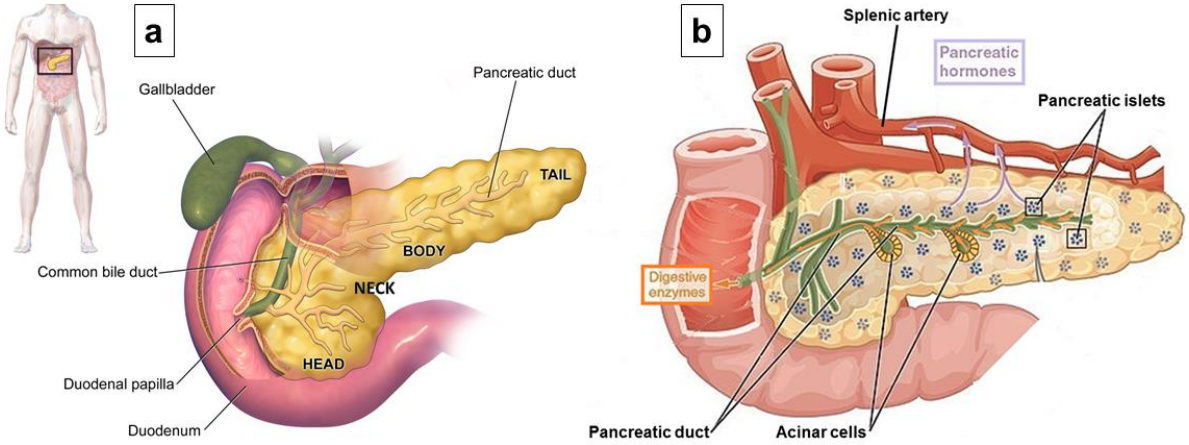

Figure 1.1: (a) Location and anatomy of the pancreas (colored in yellow). Modified from Wikiversity Journal of Medicine (en.wikiversity.org/wiki/Wikiversity_Journal_of_Medicine/Blausen_gallery_2014) (CC BY); and (b) exocrine and endocrine function of the pancreas. Modified from OpenStax College (cnx.org/content/col11496/1.6) (CC BY).

[1]A gland is an organ that synthesizes and releases a substance inside the body (via the bloodstream, so-called endocrine secretion) or onto an outer surface of the body (via a duct, so-called exocrine secretion).

1.2 Acute pancreatitis

Acute pancreatitis is a sudden inflammation of the pancreas. It may occur throughout the entire lifespan of a human, affecting the youngest of children and the oldest of adults (Morinville, Barmada, & Lowe, 2010), and has a broad spectrum of clinical outcomes, ranging from mild and self-limiting to severe and potentially fatal (Johnson, Besselink, & Carter, 2014; Lankisch, Apte, & Banks, 2015). As a common reason for hospital admissions, it also leads to substantial costs for the health care system. In 2009, for example, the number of hospitalizations due to acute pancreatitis was 274,119 in the USA (Peery et al., 2012) and 4980 in Sweden (Socialstyrelsens statistikdatabas, 2016); corresponding to estimated costs of $2.6 billion (Peery et al., 2012) and €38.5 million (Andersson et al., 2013), respectively. Upper abdominal pain, usually of abrupt onset and accompanied by nausea and vomiting, is the most typical symptom of acute pancreatitis. Its diagnosis is based on clinical symptoms, elevated concentrations of digestive enzymes, and/or disease-specific findings on radiological examinations. For a rather large percentage of patients, around 20 to 30%, the first episode of acute pancreatitis is followed by recurrent attacks and/or progression to a chronic disease state, so-called chronic pancreatitis (defined as persistent inflammation that is stable or worsens over time, causing permanent tissue damages) (Sankaran et al., 2015).

1.2.1 Pathogenesis and pathophysiology

The pathogenesis of acute pancreatitis, that is, the biological mechanism(s) that initiate its development, is not fully understood. In experimental studies, the most common induction method is infusion with supramaximal concentrations of CCK (Saluja, Lerch, Phillips, & Dudeja, 2007).[2] (Supramaximal refers to a concentration well above that required for maximal secretion of the digestive enzyme amylase.) However, there is no evidence that such concentrations are ever reached in humans, not even in pathological settings, because they are at least 10-fold greater than those observed in response to any type of meal (Gorelick & Thrower, 2009). It has, therefore, been hypothesized that one way by which genetic and environmental factors might be involved in the pathogenesis of acute pancreatitis is by sensitizing the pancreas to more physiological concentrations of CCK.

Similar to its pathogenesis, the biological mechanism(s) by which acute pancreatitis progresses—its pathophysiology—is only partially known.[3] Nonetheless, several pathological processes in the pancreatic acinar cell and its surrounding tissues have been identified, including (but not limited to) changed secretion, localization, and activation of the precursors of digestive enzymes as well as disturbed cell signaling and increased release of inflammatory and oxidative stress[4] markers (Sah & Saluja, 2011). Historically, the majority of experimental studies have focused on intra-acinar activation of the precursor enzyme trypsinogen to the active enzyme trypsin (which, in a normal setting, occurs as the first step in

[2]Other methods are pancreatic duct ligation and administration of a choline-deficient ethionine-supplemented diet or an extremely high dose of L-arginine.

[3]In the publications included in this thesis, I have used the term *pathogenesis* as a joint description for processes related to the pathogenesis as well as to the pathophysiology.

[4]Oxidative stress can be defined as "biochemical damage caused by attack of reactive species [chemically reactive molecules containing oxygen or nitrogen] upon the constituents of living organisms" (Halliwell & Gutteridge, 2007).

the duodenal activation of digestive enzymes), and it is still seen as the central event in the pathophysiology of acute pancreatitis (Gorelick & Thrower, 2009; Sah & Saluja, 2011; Saluja et al., 2007; Waldthaler, Schütte, & Malfertheiner, 2010). Indeed, intra-acinar activation of trypsinogen has been shown to lead to acinar cell death during the early phases of acute pancreatitis, being responsible for around 50% of the eventual damage (Dawra et al., 2011). However, it is becoming increasingly clear that there are other mechanisms that might be equally important, especially the nuclear factor kappa-light-chain-enhancer of B cells (NFκB) pathway,[5] because of the findings that local and systemic inflammation progresses independently of trypsinogen during the course of acute pancreatitis (Sah, Dawra, & Saluja, 2013).

1.2.2 Clinical aspects

1.2.2.1 Diagnosis and diagnostics tests

As previously mentioned, the cardinal symptom of acute pancreatitis is an abrupt onset of severe and persistent upper abdominal pain, which often radiates to the lower areas of the middle back (Johnson et al., 2014; Lankisch et al., 2015). Nausea and vomiting are also frequent symptoms, although not prerequisites for the disease. Its diagnosis is confirmed by increased concentrations of amylase or lipase (at least 3 times the upper normal limit) or, if there are any diagnostic doubts, by disease-specific findings on radiological examinations (eg, computed tomography scan or magnetic resonance imaging) (Figure 1.2). Current international guidelines state that a diagnosis of acute pancreatitis is fulfilled when 2 out of 3 disease criterion (ie, pain, enzymes, and/or radiology) are co-existing (Banks et al., 2013; Tenner, Baillie, DeWitt, & Vege, 2013; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). In addition, it is recommended that abdominal ultrasonography is performed as soon as possible after admission, preferably within 24 hours, so that any evidence of existing or prior gallstones can be obtained, because they might have obstructed the duodenal papilla and led to development of the disease. The concentrations of liver enzymes can be increased for the same reason and should, therefore, be measured too. Additional laboratory tests are used to predict or determine the severity of acute pancreatitis as well as to identify other factors that might have been involved in its development (eg, hypercalcemia [Frick, 2012] and hypertriglyceridemia [Lindkvist, Appelros, Regnér, & Manjer, 2012]).

1.2.2.2 Classifications

According to the International Classification of Diseases (ICD), 10th revision,[6] there are 6 clinical classifications of acute pancreatitis: "biliary", "alcohol-induced", "idiopathic", "drug-induced", "other", and "unspecified". Of these, the most common classification is biliary or, as it is also known and hereinafter referred to in this thesis, gallstone-related. As a consequence, for practical as well as biological reasons, an episode of acute pancreatitis is often classified as gallstone-related or non-gallstone-related (Figure 1.3).

---

[5] NFκB is a protein complex that regulates inflammatory genes. Its inflammatory pathway has been extensively described in the pancreatic acinar cell (Rakonczay, Hegyi, Takács, McCarroll, & Saluja, 2008).

[6] ICD is the "standard diagnostic tool for epidemiology, health management, and clinical purposes" (World Health Organization, 2016) and is designed to provide diagnostic codes for classification of various diseases.

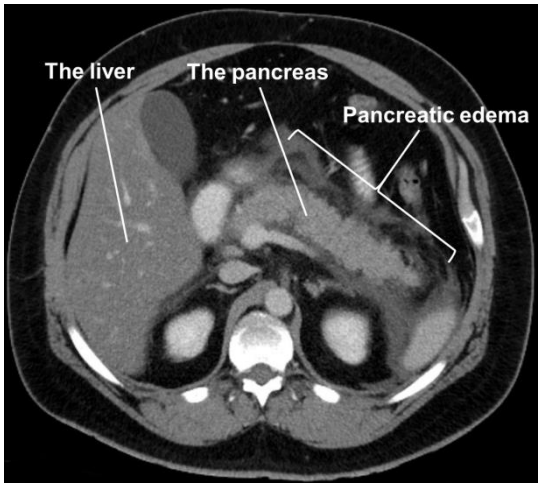

Figure 1.2: Computed tomography scan of a patient with acute pancreatitis. The pancreatic edema gives the pancreas a "blurry" appearance. Modified from Wikimedia Commons (commons.wikimedia.org/wiki/File:Pankreatitis_exsudativ_CT_axial.jpg) (CC BY SA).

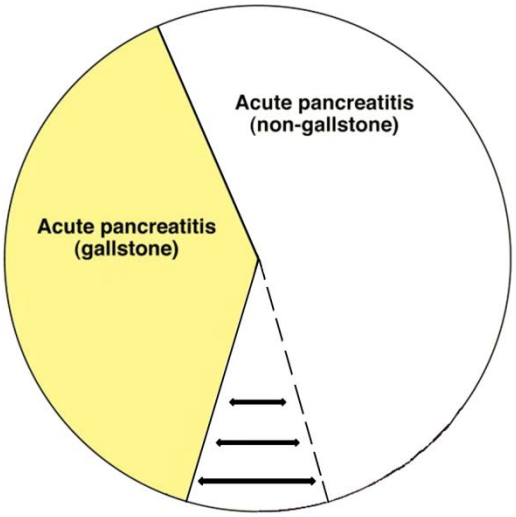

Figure 1.3: Proportion of all episodes that are classified as gallstone-related or non-gallstone-related acute pancreatitis. The black arrows and the dashed line indicate the proportion variation in 3 Swedish studies with access to medical charts (publication details are available in the Supplementary material). Modified from Yadav & Lowenfels (2013) with permission of Elsevier.

In turn, according to the revised Atlanta classification (Banks et al., 2013),[7] the severity of acute pancreatitis can be divided into 3 categories: "mild" (no organ failure[8] of the respiratory, cardiovascular, or renal system and no local or systemic complications), "moderately severe" (short-time organ failure [≤48 hours] or local or systemic complications), and "severe" (persistent organ failure [>48 hours]). (Examples of local pancreatic complications are necrosis [pathological cell death] and pseudocysts [cyst-like lesions containing pancreatic fluid] and examples of systemic complications are exacerbations of pre-existing diseases, such as chronic liver and lung diseases.) While, at least, 80% of all patients fall into the mild category and require a short hospital stay (Oskarsson et al., 2011; Swaroop, Chari, & Clain, 2004), there is still a large and significant number of patients who fall into the severe category, especially since they have a high mortality (30%) and require a long hospital stay with plenty of health care resources (Petrov, Shanbhag, Chakraborty, Phillips, & Windsor, 2010).

1.2.2.3 Management and secondary prevention

There is, to date, no specific drug therapy for acute pancreatitis (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). Instead, the treatment is based on fluid resuscitation, pain relief, and nutritional support—the extent, type, and time of which depends on the disease severity and the patient's response. In parallel, any complication of systemic, local, or extrapancreatic nature (eg, infections in the blood stream or in the urinary tract) must be dealt with in an appropriate manner. Early

[7]The original Atlanta classification, which was the result of a symposium in Atlanta in 1992, has long been considered the "gold standard" for severity classification. A revised version was published in 2012.
[8]Organ failure occurs when an organ does not perform to its expected function.

endoscopic retrograde cholangiopancreatography (ERCP)[9] should be considered in patients with gallstone-related acute pancreatitis if they have an infection of the common bile duct (so-called cholangitis) and/or an obstruction thereof. (For more details on the acute phase management of acute pancreatitis, which is beyond the scope of this thesis, please see the recently published review articles by Johnson et al. [2014] and Lankisch et al. [2015].)

With respect to the secondary prevention of acute pancreatitis, that is, the measures that aim to reduce its recurrence and/or progression, it is recommended by current international guidelines to perform a cholecystectomy (surgical removal of the gallbladder) as a definitive treatment for patients with gallstone-related acute pancreatitis; preferably during the index admission and definitely no later than 6 weeks after discharge (Tenner et al., 2013; UK Working Party on Acute Pancreatitis, 2005; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). Most experts also agree that all patients should receive alcohol counseling, irrespective of the classification and severity of their disease, and that comorbid conditions like hypercalcemia and hypertriglyceridemia should be treated. Radiological examinations, including computed tomography scan (if not done before), endoscopic ultrasonography, and magnetic resonance cholangiopancreatography, are indicated in some patients to examine the presence of very small gallstones, malignancies, chronic pancreatitis, and anatomical abnormalities.

1.2.2.4 Long-term complications

Several long-term complications have been observed in patients with acute pancreatitis, especially in those who have a severe disease course. Apart from having a high mortality (30%) (Petrov et al., 2010) and a high development of recurrent and progressive pancreatic disease (22% and 10%, respectively) (discussed in detail in later subsections) (Sankaran et al., 2015), their quality of life (Pendharkar, Salt, Plank, Windsor, & Petrov, 2014) and exocrine and endocrine functions might also be impaired (29% and 37%, respectively) (Das, Kennedy, et al., 2014; Das, Singh, et al., 2014). Although some degree of this pancreatic insufficiency seems to be short-term in duration, at least for the exocrine part of the pancreas, meaning that there is subsequent functional recovery (Das, Kennedy, et al., 2014); it is noteworthy that more than one-fifth of all patients with acute pancreatitis develop type 2 diabetes (Das, Singh, et al., 2014), indicating substantial and persistent damages to the endocrine part of the pancreas.

1.2.3 Descriptive epidemiology

Epidemiological[10] studies have indicated large worldwide geographical variations (up to 5 times) in the incidence rate[11] of acute pancreatitis (Figure 1.4). Between-study comparisons are, however, halting because of non-consistent definitions of incident acute pancreatitis (first episodes; first and recurrent episodes; or first, recurrent, and acute-on-chronic episodes) and a lack of standardization to a common

[9]ERCP is an invasive imaging technique in which the operator can reach the duodenum and duodenal papilla via the mouth and stomach. It can be used as both a diagnostic and a therapeutic procedure.
[10]Epidemiology can be defined as the study of "the distribution and determinants of disease" (Rothman, 2012).
[11]In medicine, the term *incident* refers to the first occurrence of an event (eg, a disease or a treatment); and the term *incidence rate* refers to the number of incident events in an at-risk population under a given time period.

reference population (the observed variations could, therefore, be largely explained by differences in the populations' sex and age structures).

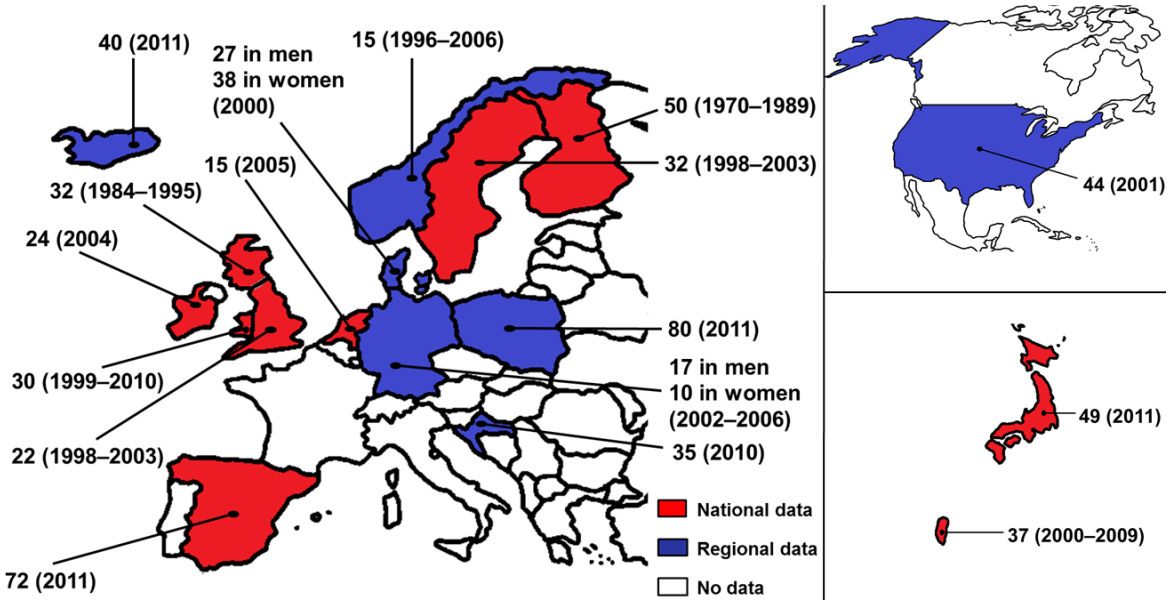

Figure 1.4: Annual incidence rate of acute pancreatitis per 100,000 persons in Europe (left), the USA (top right), and Japan and Taiwan (bottom right) (study periods in parentheses). Note that between-study comparisons are limited because of non-consistent definitions of incident acute pancreatitis (first episodes; first and recurrent episodes; or first, recurrent, and acute-on-chronic episodes) and a lack of standardization to a common reference population. Publication details are available in the Supplementary material. Modified from Wikimedia Commons (commons.wikimedia.org/wiki/File:The_World_map.png) (CC BY SA).

In Sweden, based on data from Socialstyrelsen, the national incidence rate of acute pancreatitis was estimated to be 32 cases (33 in men and 31 in women) per 100,000 persons and year during the period 1998 to 2003 (Sandzén et al., 2009).[12] Two caveats of that estimation, at least from my personal point of view, were that the authors defined incident disease as "acute pancreatitis, without hospital visit with this diagnosis, during a minimum of one year preceding index admission" and that they did not account for acute-on-chronic pancreatitis. As such, the incidence of acute pancreatitis could have been overestimated. However, similar incidence rates were seen in a large, regional study from Malmö that looked at truly incident cases, who also had no history of underlying chronic pancreatitis (approximately 34, 28, and 37 cases per 100,000 persons in 1997, 1998, and 1999, respectively) (Lindkvist, Appelros, Manjer, & Borgström, 2004). Both studies found that the incidence of acute pancreatitis had increased constantly from the mid-80s to the late-90s and the early-00s, especially in women. A similar increase in incidence has also been reported in international studies (Yadav & Lowenfels, 2006). To give an "up-to-date" picture of the descriptive epidemiology in Sweden, the age- and sex-specific diagnosis rate[13] of acute pancreatitis during the last 10-year period (2005 to 2014) is shown in Figure 1.5.

[12]To my knowledge, there is no later incidence study from Sweden.
[13]Not to be confused with the incidence rate, since the diagnosis rate includes incident, recurrent, and acute-on-chronic episodes as well as any readmission thereof.

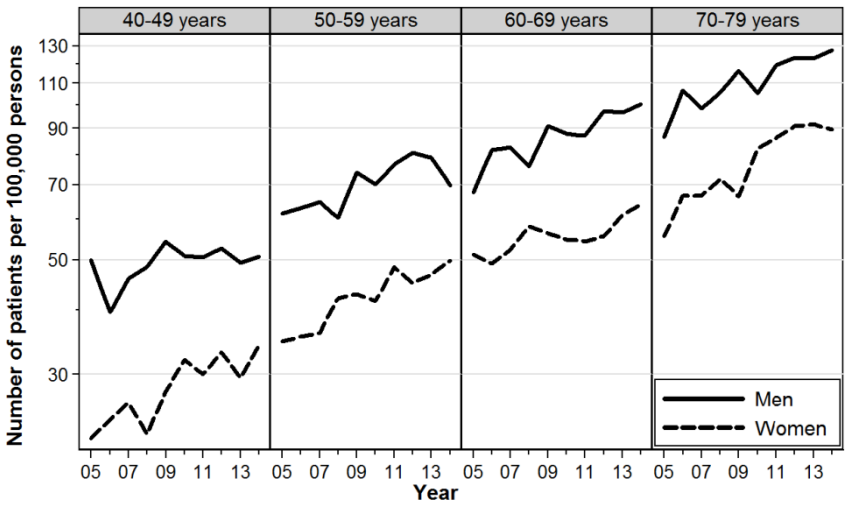

Figure 1.5: Annual diagnosis rate of acute pancreatitis (incident, recurrent, and acute-on-chronic episodes as well as any readmission thereof) per 100,000 persons in Sweden, 2005 to 2014, conditional on sex and age. Data were obtained from Socialstyrelsens statistikdatabas (2016).

In recent studies on the natural history of incident acute pancreatitis (published since 2009 and conducted in Europe and the USA), the risk[14] of recurrent disease was on average 20% (range 17 to 23%) and the risk of progression to chronic disease was on average 6% (range 4 to 8%) (Ahmed Ali et al., 2016; Bertilsson, Swärd, & Kalaitzakis, 2015; Cavestro et al., 2015; Lankisch et al., 2009; Yadav, O'Connell, & Papachristou, 2012). In Sweden, based on data from a large, regional study from Malmö and Lund, the corresponding estimates were 23% and 5%, respectively, during the period 2003 to 2013 (overall rate of 5 cases of recurrent or chronic disease per 100 persons and year) (Bertilsson et al., 2015). In general, recurrent and progressive pancreatic disease develops in patients with non-gallstone-related acute pancreatitis (exemplified in Figure 1.6), with a substantially lower risk after gallstone-related episodes (12%), especially if the recommendations for cholecystectomy have been followed (8%).

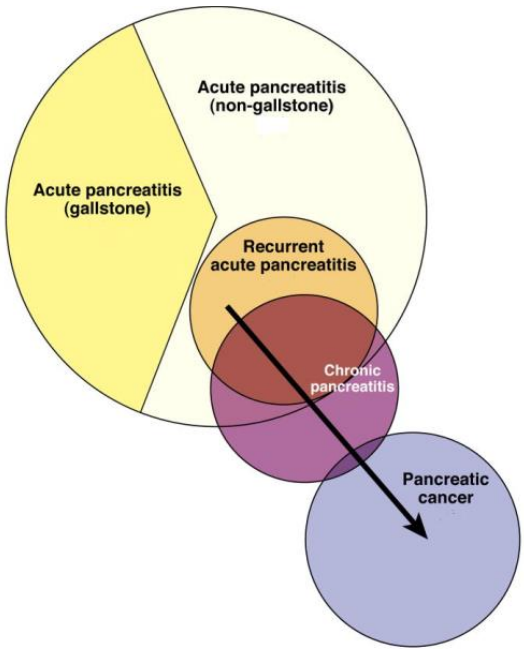

Figure 1.6: The natural history of incident acute pancreatitis according to its subtypes (gallstone-related and non-gallstone-related). The black arrow indicates the relationship between benign and malignant disease. Recurrent and progressive pancreatic disease develops predominately in patients with non-gallstone-related episodes, although it can develop in patients with gallstone-related episodes if cholecystectomy has been delayed or refused. Reproduced from Yadav & Lowenfels (2013) with permission of Elsevier.

[14]The risk (or probability) of an event is calculated as the number of events divided by the at-risk population. In this thesis, I will also use it as a generic term for other measures of occurrence (eg, incidence, odds, and hazard).

1.2.4 Analytical epidemiology (risk factors)

According to its medical subject headings (MeSH)-term,[15] a risk factor is defined as "an aspect of personal behavior or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiologic evidence, is known to be associated with a health-related condition". So, with that in mind, what are the risk factors for acute pancreatitis? The most important ones are considered to be gallstones (as already touched upon in earlier subsections) and alcohol abuse, with many pancreatic specialists concluding that "the commonest [causes]... being gallstones (50%) and alcohol (25%)" (Johnson et al., 2014) and "[gall]stones (38%) and alcohol abuse (36%) are the most frequent causes" (Frossard, Steer, & Pastor, 2008). (Although, in my opinion, such statements are somewhat misleading; a clinical observation of gallstones and/or alcohol abuse does not necessarily equal them to being the causes of the disease, at least not the sole causes.) The role of different amounts, types, and drinking patterns of alcoholic beverages is, however, less known. A Danish study found a positive association[16] between consumption of beer (≥14 drinks/week), but not of wine or spirits (irrespective of amount), and risk of any pancreatitis (Kristiansen, Grønbaek, Becker, & Tolstrup, 2008). In contrast, only the number of spirit drinks consumed at a single occasion had a positive association with acute pancreatitis in a Swedish study (Sadr-Azodi, Orsini, Andrén-Sandberg, & Wolk, 2011). In a recent dose-response meta-analysis[17] by Samokhvalov, Rehm, & Roerecke (2015), it was concluded that the risk of acute pancreatitis increased in a linear fashion with increasing alcohol intake in men but not in women, for whom an inverse association was observed for intakes up to 40 g/day. Although intuitively surprising—as all conventional wisdom states that alcohol intake should increase the risk—it must be noted that alcohol intake has been inversely associated with risk of gallstone disease (Leitzmann et al., 2003; Leitzmann, Giovannucci, et al., 1999). Thus, given that gallstone disease (including gallstone-related acute pancreatitis) is more common in women (Portincasa, Moschetta, & Palasciano, 2006; Yadav & Lowenfels, 2013), it might be there are sex differences in the alcohol-acute pancreatitis association, especially if the subtypes of acute pancreatitis are not accounted for (ie, gallstone-related vs. non-gallstone-related).

A plethora of other risk factors have been suggested for acute pancreatitis during the last decades, all with more or less evidence for having such a role, and some of them are shown in Table 1.1. Special mention should be given to cigarette smoking and type 2 diabetes, both of which has had positive associations in far more publications than those listed in Table 1.1 (including meta-analyses [Sun, Huang, Zhao, Chen, & Xie, 2015; Yang, He, Tang, & Liu, 2013]). Smoking has also been associated with a higher risk of recurrent and progressive pancreatic disease (Ahmed Ali et al., 2016; Bertilsson et al., 2015), as has a clinical classification of alcohol-related acute pancreatitis (Bertilsson et al., 2015; Yadav et al., 2012) and a severe disease course (Ahmed Ali et al., 2016; Bertilsson et al., 2015).

---

[15] MeSH is a controlled descriptive vocabulary for the purpose of indexing books and journal articles (ncbi.nlm.nih.gov/mesh/68012307).

[16] Analytical epidemiology commonly evaluates the association between an exposure and the risk of developing a health-related outcome, presenting the results according to relative change. The terms *positive* (higher risk) and *inverse* (lower risk) refer to the direction of an association.

[17] A meta-analysis is an "analysis of analyses", combining results of several independent studies.

Table 1.1: Selected potential risk factors for acute pancreatitis (other than gallstones and alcohol abuse)*

Risk factor	Direction of association	Reference(s)
Non-modifiable		
Male sex	Dual†	Sandzén et al. (2009); Yadav & Lowenfels (2013)
Old age	Positive	Sandzén et al. (2009); Yadav & Lowenfels (2013)
Black race/ethnicity	Dual†	Frey, Zhou, Harvey, & White (2006); Yang, Vadhavkar, Singh, & Omary (2008)
Gene mutations‡	Positive	Ballard et al. (2015); Keiles & Kammesheidt (2006)
Anatomical abnormalities	Positive	Feller (1984); Zyromski et al. (2008)
Modifiable		
Cigarette smoking§	Positive	Lindkvist, Appelros, Manjer, Berglund, & Borgstrom (2008); Sadr-Azodi, Andrén-Sandberg, Orsini, & Wolk (2012)
Obesity/adiposity	Positive	Lindkvist et al. (2008); Sadr-Azodi, Orsini, Andrén-Sandberg, & Wolk (2013)
Type 2 diabetes	Positive	Girman et al. (2010); Noel, Braun, Patterson, & Bloomgren (2009)
Hypertriglyceredemia§	Positive	Lindkvist et al. (2012); Murphy, Sheng, MacDonald, & Wei (2013)
Autoimmune diseases¶	Positive	Sadr-Azodi, Sanders, Murray, & Ludvigsson (2012); Chang et al. (2015)
Inflammatory diseases‖	Positive	Chen et al. (2016); Lai, Lai, Lin, Liao, & Tseng (2015)
Cardiovascular diseases	Positive	Bexelius, Ljung, Mattsson, & Lagergren (2013); Lai et al. (2015)
Use of medical drugs¥	Positive	See footnote ¥
ERCP	Positive	Ding, Zhang, & Wang (2015)

ERCP, endoscopic retrograde cholangiopancreatography.
*In the case of more than 2 publications on the same risk factor, I chose the ones that were most relevant in terms of geographical origin (Sweden before other parts of the world), definition of acute pancreatitis (incident before recurrent disease), and publication date (newer before older).
†Male sex and black race/ethnicity have been associated with a higher risk of non-gallstone-related acute pancreatitis and with a lower risk of gallstone-related acute pancreatitis.
‡The most commonly described mutations are variants in the PRSS1, SPINK1, and CFTR genes.
§Indications (if examined) that the exposure-outcome association is substantially stronger in, or even restricted to, non-gallstone-related acute pancreatitis.
¶Celiac disease and rheumatoid arthritis.
‖Inflammatory bowel disease and chronic osteomyelitis.
¥More than 100 drugs have been alleged to cause acute pancreatitis (Badalov et al., 2007), including postmenopausal hormones (Oskarsson, Orsini, Sadr-Azodi, & Wolk, 2014), oral corticosteroids (Sadr-Azodi, Mattsson, et al., 2013), and antibiotics (Ljung, Lagergren, Bexelius, Mattsson, & Lindblad, 2012).

1.3 Diet and health

The food and beverage choices that we make on a daily basis have a profound influence on our long-term health. A recent report from the Global Burden of Disease collaboration (Forouzanfar et al., 2015) estimated that dietary risks (defined as the aggregation of 14 specific dietary patterns, including low fruit, low vegetables, and high meat) accounted for 11.3 million deaths and 241.4 million disability-adjusted life-years (DALYs)[18] worldwide in 2013. Even though diet already had the largest contribution to the DALYs (Figure 1.7), the authors of the report concluded that "[i]f one were to quantify the contribution of diet mediated through weight gain and [body mass index], the overall effect of diet would be much larger".

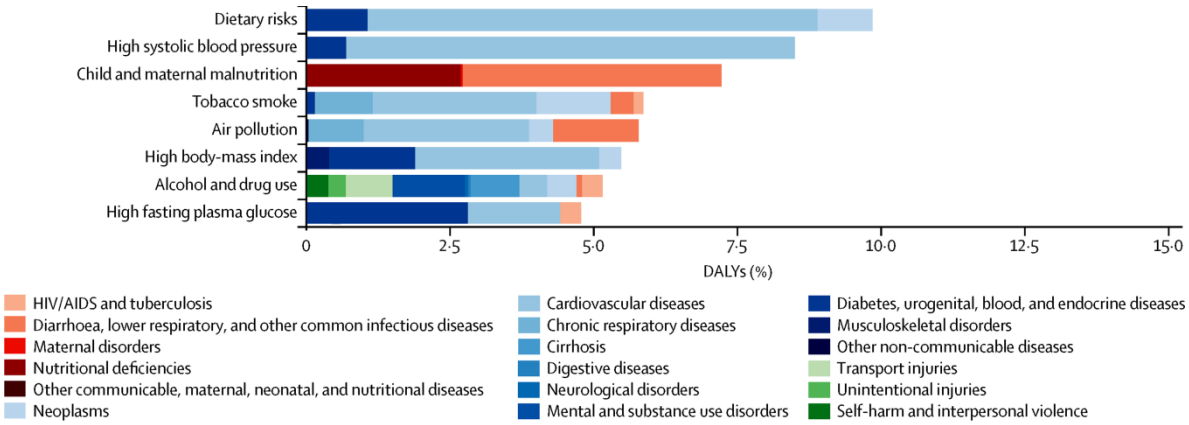

Figure 1.7: Global DALYs attributed to various risk factors in both sexes combined, 2013. Modified (by omitting risk factors with a lower contribution than that of high fasting plasma glucose) from Forouzanfar et al. (2015) with permission of Elsevier.

1.3.1 Fruit and vegetables

The health benefits of a diet high in fruit and vegetables are established and well known. Inverse associations have been observed with, amongst others, type 2 diabetes (Carter, Gray, Troughton, Khunti, & Davies, 2010), cardiovascular diseases (Hartley et al., 2013), cancers (Aune et al., 2011; Lunet, Lacerda-Vieira, & Barros, 2005), and overall mortality (Bellavia, Larsson, Bottai, Wolk, & Orsini, 2013). Although consumption of fruit and vegetables is often studied as a joint exposure variable, there is increasing evidence that they should be treated as separate food items, because of differences in their bioactive compounds and in their associations with (some) health-related outcomes (Appleton et al., 2016). In Sweden, the dietary recommendation is that, at least, 500 g of fruit and vegetables (around 5 servings) are consumed per day (Konde et al., 2015).

1.3.2 Glycemic load

Glycemic load is a measure that takes into account the amount of carbohydrates in a particular food item, together with how the same food item influences postprandial[19] concentrations of glucose and insulin (the so-called glycemic index [Jenkins et al., 1981]) (Salmeron et al., 1997). It has been associated with

[18]DALY is a measure of overall disease burden that is expressed as the number of years lost due to ill-health, disability, or early death.
[19]After ingestion of a meal.

higher risks of developing major chronic diseases, such as type 2 diabetes (Bhupathiraju et al., 2014), cardiovascular diseases (Mirrahimi et al., 2014), and cancers (Turati et al., 2015), as well as with a higher overall mortality (Baer et al., 2011; Castro-Quezada et al., 2014). The Swedish dietary guidelines states that whole grain products of pasta, bread, grains, and rice (which have a low glycemic index) should be chosen instead of processed products (which have a high glycemic index) (Konde et al., 2015).

1.3.3 Fish

Different studies have suggested that fish consumption, which, broadly, can be divided into that of fatty fish and that of lean fish according to the content of long-chain n-3 polyunsaturated fatty acids (LCn-3 PUFAs), has an inverse association with various chronic diseases (Di Giuseppe, Wallin, Bottai, Askling, & Wolk, 2014; Djoussé, Akinkuolie, Wu, Ding, & Gaziano, 2012; Kolahdooz et al., 2010; Larsson & Orsini, 2011; Yu, Zou, & Dong, 2014) and overall mortality, especially with mortality due to cardiovascular diseases (Zhao et al., 2016; Zheng et al., 2012). A fish consumption of 2–3 servings/week, of which 1 serving should be fatty fish, is recommended in Sweden (Konde et al., 2015).

1.3.4 Coffee

Coffee consumption was for a long time considered to be an unhealthy lifestyle habit; however, this conception has slowly changed during the last decades and is almost reversed today. In addition to being associated with a lower overall mortality (Crippa, Discacciati, Larsson, Wolk, & Orsini, 2014), coffee consumption appears to reduce the risk of type 2 diabetes (Ding, Bhupathiraju, Chen, van Dam, & Hu, 2014), cardiovascular diseases (Ding, Bhupathiraju, Satija, van Dam, & Hu, 2014), and cancers (Bøhn, Blomhoff, & Paur, 2014). There is, to date, no dietary recommendation for coffee consumption in Sweden.

1.3.5 Recommended food score

The recommended food score (RFS) is an indicator of overall diet quality (Kant, Schatzkin, Graubard, & Schairer, 2000).[20] It includes a number of healthy food items, such as vegetables and fruits, fish, and whole grains; all of which are recommended by international and national dietary guidelines. Overall mortality (Kaluza, Håkansson, Brzozowska, & Wolk, 2009; Kant et al., 2000), as well as risks of major chronic diseases, particularly cardiovascular diseases (Larsson, Åkesson, & Wolk, 2014; McCullough et al., 2002), has been inversely associated with both the original RFS and a number of its adapted versions. An advantage of studying a dietary pattern—and not a single food item or nutrient—is that it accounts for the fact that food items and nutrients might have synergistic and/or antagonistic effects[21] on health.

[20]Other examples of such indicators are the Mediterranean-diet score, the Healthy Eating Index, and the Dietary Approaches to Stop Hypertension diet.

[21]The term *synergy* refers to a situation when the sum of a whole is greater than the sum of its individual parts; and vice versa, for the term *antagonism*.

1.4 Diet and risk of acute pancreatitis

The epidemiological literature on the association between diet and risk of acute pancreatitis is, to say the least, sparse. Furthermore, it is often unclear what type (incident, recurrent, or acute-on-chronic) and subtype (gallstone-related or non-gallstone-related) of acute pancreatitis that has been studied. In the 60's and 70's, Sarles[22] and colleagues published one case-control study (French data) (Sarles et al., 1965) and one ecological study (European, American, Asian, and African data) (Sarles, 1973) detailing intakes of protein, fat, and carbohydrates in relation to risk and mortality of acute pancreatitis. These studies were followed by a small number of case-control and ecological studies in the 80's and 90's, which, also, examined intakes of protein, fat, and carbohydrates—either on the risk of alcohol-related or gallstone-related acute pancreatitis (Australian data) (Wilson et al., 1985), on the risk of non-gallstone-related acute pancreatitis (Swedish data) (Schmidt, 1991), or on the mortality of acute pancreatitis (European, American, Asian, and African data) (Niederau, Niederau, & Strohmeyer, 1988). Overall, there was no indication that these nutrients had a strong role, if any, in the development of acute pancreatitis. Then, in the 00's and early 10's, one large, prospective US cohort study[23] observed an inverse association between coffee consumption and risk of alcohol-related acute pancreatitis (Morton, Klatsky, & Udaltsova, 2004); whereas 2 small case-control studies (from South Africa and India, respectively) reported associations of consumption of fruit (inverse in direction) (Segal, Charalambides, Becker, & Ally, 2000), fresh water fish, and parboiled rice (both positive in direction) (Mitta, Barreto, & Rodrigues, 2011) with risk of acute pancreatitis. (It should be noted, however, that the authors of the latter study concluded that "[o]ther foods [apart from fresh water fish and parboiled rice]… had no significant association", which, as was evident in a re-analysis that I did, is clearly incorrect; both consumption of beef and mutton had significant inverse associations.) In parallel, there has been suggestions and anecdotal evidence of extremely large meals (around 2000 kcal) after a long period of fasting (Gao et al., 2007) and food allergies (Matteo & Sarles, 1990) as risk factors for acute pancreatitis.

In a review article by Yadav and Lowenfels (2013), the role of diet in the development of acute and chronic pancreatitis was quoted as "an important area for future research". Since then, the largest and most well-conducted studies on the association between diet and risk of acute pancreatitis have been published (together with the above mentioned study by Morton et al. [2004] and including **Paper I–V** of this thesis; all of which will be presented and discussed in the forthcoming chapters). In a large cross-sectional study from China, a high-meat dietary pattern (defined as a diet "containing more than 50% of the flesh of animals") had a positive association with risk of acute pancreatitis, even though it was attenuated after controlling for other risk factors (Yang et al., 2014). Several nutrients (eg, fat, protein, and carbohydrates) and some food items (ie, fruit and vegetables; and meat) were examined in the Iowa Women's Health

[22]Henri Sarles (b. 1922) is somewhat of a legend in pancreatic research, with multiple publications on the role of nutritional factors in the development of pancreatic diseases. An interview with him from 2008 is available via pancreapedia.org/sites/www.pancreapedia.org/files/2008-sarles.pdf

[23]A prospective cohort study, which is the study design used in **Paper I–V**, assesses an exposure at the beginning of an observational period (follow-up period) and then follows participants prospectively until they experience the outcome of interest (Rothman, 2012). The other types of study designs mentioned here (case-control, ecological, and cross-sectional) will be explained in later chapters.

Study, a large cohort of older US women, of which fat intake had a positive association with risk of acute pancreatitis (Prizment, Jensen, Hopper, Virnig, & Anderson, 2015). Furthermore, in a recently published conference abstract that used data from more than 140,000 US men and women, who were enrolled in the Multiethnic Cohort, it was reported that "[d]ietary intakes of saturated fat and cholesterol, and their food sources (eg, red meat, eggs, and shellfish), were positively associated with pancreatitis, whereas intakes of fiber, vitamin D, and coffee were inversely associated with variation by pancreatitis types" (Setiawan et al., 2015). A high-fat diet was also associated with a higher risk of gallstone-related acute pancreatitis in a small case-control study of pregnant Chinese women (Jin, Yu, Zhong, & Zhang, 2015). Of note, however, is that no study has examined the role of diet in the natural history of acute pancreatitis; that is, how diet might affect the risk of recurrent and progressive pancreatic disease after an incident episode of acute pancreatitis.[24]

While the association between diet and risk of acute pancreatitis is understudied, the same cannot be said about diet and risk of symptomatic gallstone disease. In several epidemiological studies, many of which have been conducted in large prospective cohorts, such as the Nurses' Health Study and the Health Professionals Follow-Up Study,[25] the risk of symptomatic gallstone disease has been altered by, for example, fruit and vegetable consumption (lower risk) (Nordenvall, Oskarsson, & Wolk, 2016; Tsai, Leitzmann, Willett, & Giovannucci, 2006), high-glycemic load foods (higher risk) (Tsai, Leitzmann, Willett, & Giovannucci, 2005a, 2005b), and coffee drinking (lower risk) (Leitzmann et al., 2002; Leitzmann, Willett, et al., 1999; Nordenvall, Oskarsson, & Wolk, 2015). In all of the mentioned studies, symptomatic gallstone disease was defined as having undergone a cholecystectomy (either as the main outcome measure or as the "gold standard" in sensitivity analyses)—that is to say, the same surgical procedure that current international guidelines recommended as the definitive treatment for all patients with gallstone-related acute pancreatitis (Tenner et al., 2013; UK Working Party on Acute Pancreatitis, 2005; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).

[24]Except for a few (and small) studies that have described potential beneficial effects of dietary changes in the presence of celiac disease and/or extreme hypertriglyceridemia (Patel, Johlin, & Murray, 1999; Sandhu, Al-Sarraf, Taraboanta, Frohlich, & Francis, 2011). These studies will not be mentioned hereinafter.

[25]The Nurses' Health Study (channing.harvard.edu/nhs) and the Health Professionals Follow-Up Study (hsph.harvard.edu/hpfs), managed by Harvard University in the USA, are, arguably, the 2 most famous and influential prospective cohort studies in the field of nutritional epidemiology.

2 Aims

The overall aim of this thesis was to study the association between diet and risk of non-gallstone-related acute pancreatitis.

More specifically, the aim of each study was:

Paper I – To study, prospectively, the association of fruit and vegetable consumption with incidence of non-gallstone-related acute pancreatitis in a large cohort of men and women.

Paper II – To study, prospectively, the association between glycemic load and incidence of non-gallstone-related acute pancreatitis in a large cohort of men and women.

Paper III – To study, prospectively, the association of total fish consumption, as well as that of fatty fish and lean fish separately, with incidence of non-gallstone-related acute pancreatitis in a large cohort of men and women.

Paper IV – To study, prospectively, the association between coffee drinking and incidence of non-gallstone-related acute pancreatitis in a large cohort of men and women.

Paper V – To study, prospectively, the association between overall diet quality (calculated using a recommended food score) and risk of recurrent and progressive pancreatic disease in a cohort of men and women with non-gallstone-related acute pancreatitis.

3 Material and methods

3.1 Study population

This thesis was based on data from a large group of middle-aged and elderly persons from central Sweden, who were enrolled in 2 prospective studies, the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM), and who were followed up via linkage to relevant national health registers (see below). A detailed description of the SMC and the COSM has been given by Harris et al. (2013) and is also available online (ki.se/en/imm/unit-of-nutritional-epidemiology). Detailed descriptions of the Swedish National Patient Register (SNPR), the Swedish National Cancer Registry, the Swedish National Cause of Death Register (on the website of Socialstyrelsen[26]), and the Swedish National Diabetes Register (ndr.nu/#/english) are likewise available online. The Regional Ethical Board at Karolinska Institutet approved **Paper I–V** (dnr 2010/1091-31/1 and dnr 2014/2032-32).

3.1.1 The Swedish Mammography Cohort and the Cohort of Swedish Men

Recruitment to the SMC took place in 1987 to 1990, with a final sample of 66,651 women (born 1914 to 1948) from Uppsala and Västmanland counties (Figure 3.1). At baseline, they filled in a questionnaire about diet and lifestyle habits. Subsequent questionnaires were sent in 1997 and in 2009, to which 39,227 and 25,332 of the original women answered. Recruitment to the COSM took place in 1997, with a final sample of 48,850 men (born 1918 to 1952) from Örebro and Västmanland counties. At baseline, they filled in the same questionnaire as women had done in 1997 (apart from sex-specific questions) and 26,156 of them answered the subsequent questionnaire in 2009. Since the first female questionnaire did not contain questions on some important factors, including cigarette smoking and physical activity, I only used questionnaire data from 1997 (main analyses in **Paper I–V**) and 2009 (sensitivity analyses in **Paper V**).[27]

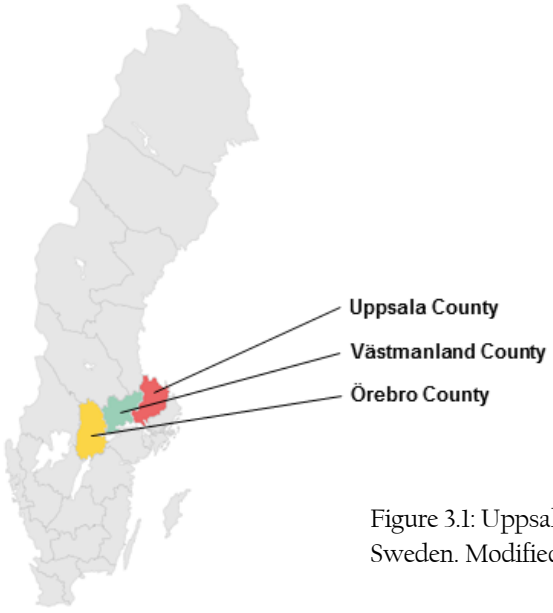

Figure 3.1: Uppsala, Västmanland, and Örebro counties in central Sweden. Modified with permission from Wallin (2016).

[26] socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish || socialstyrelsen.se/register/halsodata-register/cancerregistret/inenglish || socialstyrelsen.se/statistics/statisticaldatabase/help/causeofdeath

[27] Since I am solely responsible for this thesis, I will use the active voice terms *I* and *my* instead of *we* and *our*.

3.1.2 National health registries

3.1.2.1 The Swedish National Patient Register

The SNPR contains information on all in-hospital and out-hospital specialist care in Sweden, including codes for diagnoses (according to the ICD) and surgical procedures (according to the Swedish version of the Nordic Medico-Statistical Committee [NOMESCO] Classification of Surgical Procedures) (Ludvigsson et al., 2011).[28] The national coverage of in-hospital data has been complete since 1987 and that of out-hospital specialist care data since 2001. With respect to county-specific coverage of in-hospital data, it has been complete since 1964, 1975, and 1985 in Uppsala, Örebro, and Västmanland counties, respectively.

3.1.2.2 The Swedish National Cancer Registry

The Swedish National Cancer Registry includes information on all primary malignancies as well as on a few benign tumors and pre-cancerous lesions. It has been shown to have a high level of completeness; for example, in 1998, the rate of non-reporting was estimated to be less than 4% (Barlow, Westergren, Holmberg, & Talbäck, 2009).

3.1.2.3 The Swedish National Cause of Death Register

The Swedish National Cause of Death Register contains information on date of death for all deceased Swedish residents, irrespective of whether they died in Sweden or not. Around 90% of all deaths are reported within 10 days and 100% are reported within 30 days (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009).

3.1.2.4 The Swedish National Diabetes Register

The Swedish National Diabetes Register comprises information on specialized (in- and out-hospital) and primary care of diabetic patients in Sweden. Its coverage has been increasing year by year and is now estimated to be 97% on a national level, albeit with substantial geographical variations (eg, 100% in Örebro and Västmanland counties but only 62% in Uppsala County) (Nationella Diabetesregistret, 2014).

[28]For diagnoses, it was possible to report 1 main diagnosis and up to 5 secondary diagnoses until 1996; a total of 8 diagnoses from 1997 to 2008; and an unlimited number of diagnoses since 2010. Similarly, there used to be a total of 12 surgical procedures that could be reported, but today that number is even higher.

3.2 Exposure assessment

Participants in the SMC and the COSM reported their average dietary intake under the previous year using a 96-item food-frequency questionnaire (FFQ) in 1997 and a 132-item FFQ in 2009. For the majority of food items, there were 8 frequency-of-consumption responses, which ranged from "never" to "3 or more times per day" (Figure 3.2, left). For some common food items, such as bread, dairy products, tea, and coffee, there were instead open-ended responses (Figure 3.2, right). Since **Paper I–V** almost exclusively used data from 1997 (only **Paper V** used data from 2009 in a sensitivity analysis), the reminder of this section will be restricted to the FFQ in 1997.

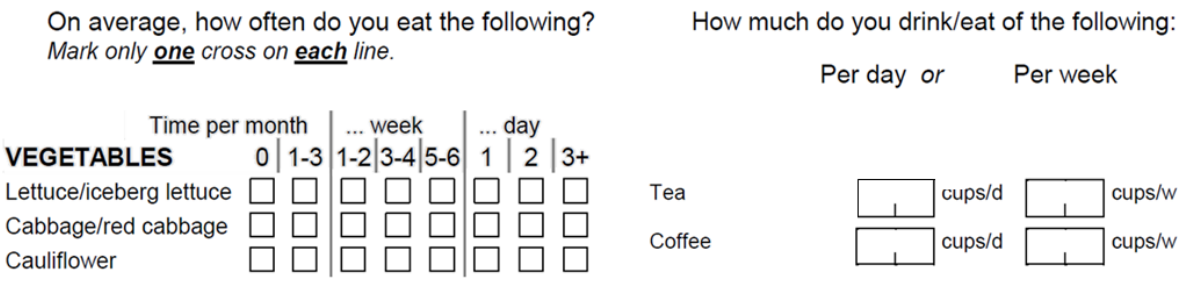

Figure 3.2: Examples of questions with frequency-of-consumption responses (left) and open-ended responses (right). Modified from the FFQ in 1997 (ki.se/sites/default/files/1997_-_smc_eng.pdf).

3.2.1 Fruit and vegetables (Paper I)

All questions related to consumption of fruit (orange and citrus fruit; orange juice; apple and pear; banana; berry; and other fruit) and vegetables (carrot; beetroot; lettuce and leafy salad; cabbage; cauliflower; broccoli and Brussels sprout; tomato and tomato juice; pepper; spinach; green peas; onion and leek; and garlic) had frequency-of-consumption responses, which were converted to an average consumption (servings/day). Variables for total fruit consumption and total vegetable consumption were, thereafter, created by aggregating the consumption of each individual item. In a validation study of 129 women,[29] the correlation between the FFQ-based estimates and those from four 1-week diet records ranged from 0.4 to 0.6 for vegetable items and from 0.5 to 0.7 for fruit items (Wolk, 1992).[30]

3.2.2 Glycemic load (Paper II)

A total score of glycemic load was calculated by (*i*) multiplying a food item's carbohydrate content (in g) (according to age- and sex-specific portion sizes) by its glycemic index score, (*ii*) multiplying that product by the number of servings/day and (*iii*) summing the glycemic loads from all individual food items in the FFQ. Values for the carbohydrate content (as well as for other nutrients and energy) were acquired from the Swedish Food Administration Database (Bergström, Kylberg, Hagman, Erikson, & Bruce, 1991), and values for the glycemic index were acquired from an international table that had white

[29]A validation study examines the extent to which a measure actually captures what it is intended to measure. For FFQs, the validity is presented as the correlation between the questionnaire of interest and a "gold standard" (eg, diet records), ranging from 0 (no correlation) to 1 (perfect correlation).
[30]Correlations on the order of 0.5 to 0.7 are quite typical for the validity of FFQ-based data (please see Table 6.6 in the textbook Nutritional Epidemiology [Willett, 2013] for details).

bread as the reference food (1 unit of glycemic load, therefore, represents the equivalent of 1 g of carbohydrate from white bread) (Foster-Powell, Holt, & Brand-Miller, 2002).[31] The FFQ-based estimate of total glycemic load (correlation = 0.8), as well as that of overall glycemic index (correlation = 0.6) and total carbohydrate intake (correlation = 0.8), has been validated by comparing it with two 1-week diet records among 141 men (Levitan, Westgren, Liu, & Wolk, 2007). Glycemic load, together with all other nutrients except alcohol, were energy-adjusted using the residual method (to 2000 kcal/day) (Willett, 2013).[32]

3.2.3 Fish (Paper III)

The FFQ had 3 questions on fish consumption, all with frequency-of-consumption responses: 2 related to fatty fish items (salmon, whitefish, and char; and herring and mackerel) and 1 related to lean fish items (cod, saithe, and fish fingers). The frequency-of-consumption response of each question was converted to an average consumption (servings/day) and combined to obtain variables for total fish consumption, fatty fish consumption, and lean fish consumption. The questions on fish consumption were validated at the same time, and in the same conditions, as those on fruit and vegetable consumption; the correlation was 0.5 for fatty fish items and 0.4 for lean fish items (Wolk, 1992).

3.2.4 Coffee (Paper IV)

Coffee consumption (in cups; 1 cup equal to 150 ml) was reported with an open-ended response question (see Figure 3.2, right, for the actual question). This question has been validated in a group of 248 men, with a correlation of 0.7 between the FFQ-based estimate and that from fourteen 24-h dietary recall interviews (Wolk, n.d.).

3.2.5 Recommended food score (Paper V)

Overall diet quality was classified according to a recommended food score (RFS) (originally developed by Kant et al. [2000] and later adapted to the FFQ in 1997 [Messerer, Håkansson, Wolk, & Åkesson, 2008]), which included the following healthy food items: fruit (n = 4 [orange and citrus fruit; apple and pear; banana; and berry]), vegetables (n = 11 [carrot; beetroot; lettuce and leafy salad; cabbage; cauliflower; broccoli and Brussels sprout; spinach; tomato and tomato juice; pepper; green peas; and mixed vegetables]), legumes (n = 1), nuts (n = 1), low-fat dairy products (n = 2 [reduced-fat milk; and reduced-fat cultured milk or yogurt]), whole grains (n = 3 [whole grain bread; crisp or hard bread; and oatmeal]), and fish (n = 3 [salmon, whitefish, and char; herring and mackerel; and cod, saithe, and fish fingers]). The RFS was calculated by summing the number of food items that were consumed at least weekly (adding up to a maximum score of 25).

[31] An alternative reference food is glucose, which, as an example, has been used by the European Prospective Investigation into Cancer and Nutrition study (van Bakel et al., 2009).
[32] The reason for such an adjustment is greatly explained by Willett (2013): "to determine whether an effect is due to a nutrient per se rather than energy intake, it is essential that the diets being compared are isocaloric".

3.3 Covariate assessment

The FFQ was used to collect information on other relevant food and beverage habits (eg, meat consumption and alcohol intake) and to calculate energy and nutrient intakes (eg, fiber and fat) as well as a non-RFS (based on 21 less healthy food items, such as sugar, sweets, and whole-fat dairy products) (Michels & Wolk, 2002). The questionnaire also contained questions on sociodemographic factors (eg, age and education), anthropometric measurements (eg, weight and height; used to calculate body mass index [BMI] [$kg \cdot m^{-2}$]), lifestyle habits (eg, cigarette smoking and physical activity), medical history of selected diseases (eg, diabetes and hyperlipidemia), and use of selected drugs (eg, corticosteroids and aspirin) and supplements (eg, multivitamins and fish oil). The female questionnaire had additional questions on, amongst others, menopausal status and use of postmenopausal hormones. Complementary data on medical histories were obtained via linkage to the SNPR and the Swedish National Diabetes Register, as were the data on clinical characteristics used in **Paper V**.

Overall, at the time of data collection in 1997, the SMC and the COSM were comparable to the Swedish population in terms of age distribution, education, BMI, and cigarette smoking (Table 3.1).

Table 3.1: Percentage distribution of selected characteristics in the study cohorts and the Swedish population in 1997

	Women, aged 55-83 years†		Men, aged 55-79 years†	
Characteristics*	**SMC**	**Swedish population**	**COSM**	**Swedish population**
Age distribution (years)				
55–59	17.9	15.0	15.9	15.6
60–64	14.5	12.7	13.1	12.5
65–69	13.5	12.7	14.1	11.6
70–74	12.4	12.7	12.4	10.8
75–79	10.1	12.1	9.9	9.2
80–83	2.9	7.3	—	—
Education‡				
>12 years	20.5	19.9	17.3	21.0
BMI >25 kg/m^2, by age group (years)				
55–64	45.7	47.4	59.1	60.3
65–74	49.7	52.0	56.8	57.0
75–83	42.9	42.3	47.5	43.0
Cigarette smoking§, by age group (years)				
55–64	20.8	21.5	23.7	22.8
65–74	13.4	16.5	22.4	17.2
75–83	7.9	7.7	22.1	13.4

BMI, body mass index; COSM, Cohort of Swedish Men; SMC, Swedish Mammography Cohort.
*Data were obtained from Harris et al. (2013) and Stackelberg (in press).
†For visual reasons, I used a common lower limit for the age range (full range: 48–83 years in women and 45–79 years in men).
‡Only reported for those aged 74 years or less since there were no population data available for older ages.
§Defined as "current cigarette smoking" in the study cohorts and as "daily cigarette smoking" in the Swedish population.

3.4 Outcome assessment

Data on acute pancreatitis were obtained via linkage[33] to the SNPR (diagnosis code of 5770, 577A, and K85 in ICD-8 [used until 1986], -9 [used until 1997], and -10 [used since 1997], respectively). The correctness of an ICD-10 code of acute pancreatitis has been shown to be high in this register (Razavi, Ljung, Lu, Andrén-Sandberg, & Lindblad, 2011), with positive predictive values (PPVs)[34] ranging from 83% (definitive disease) to 98% (probable disease). To be classified as definitive disease, the authors applied the current international recommendation that 2 out of 3 disease criterion had to be co-existing (ie, typical pain, elevated enzymes, and/or radiological findings) (Banks et al., 2013; Tenner et al., 2013; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). There was no evidence that the PPV differed by patients' sex or age, by calendar year (1998 or 2007), or by position of the diagnosis code (primary or secondary) (Razavi et al., 2011). Data on chronic pancreatic diseases (diagnosis code of 5771–9, 577B–X, and K86 and K87 in ICD-8, -9, and -10, respectively), cancer (including pancreatic cancer; diagnosis code of 157 in ICD-8 and -9 and C25 in ICD-10), and death was obtained from the SNPR, the Swedish National Cancer Registry, and the Swedish National Cause of Death Register, respectively.

To date, the available data at the Unit of Nutritional Epidemiology (Institute of Environmental Medicine, Karolinska Institutet) include information on incident acute pancreatitis from January 1, 1998 to December 31, 2014. During that period, there were a total of 891 persons (528 men and 363 women) who had received that diagnosis without having a prior history of pancreatic disease (including cancer). A comparison between the study cohorts and the Swedish population in terms of incidence rates of acute pancreatitis in 1998 to 2003 is shown in Table 3.2. Age- and sex-specific incidence rates were in general in remarkably good agreement, with the exception of women aged 50 to 59 years for whom it was markedly lower in the SMC than in the Swedish population.

Table 3.2: Annual incidence rate of acute pancreatitis per 100,000 persons in the study cohorts and the Swedish population, 1998 to 2003, conditional on sex and age. National data were obtained from Sandzén et al. (2009)

	Women		Men	
Age group	**SMC***	**Swedish population**	**COSM***	**Swedish population**
50–59 years	24.3	40.1	44.3	48.3
60–69 years	48.9	52.2	69.1	66.1
70–79 years	73.9	73.3	103.6	96.3

COSM, Cohort of Swedish Men; SMC, Swedish Mammography Cohort.
*Persons within the age range 50–79 years accounted for 89% of the follow-up time in men and 92% of the follow-up time in women.

3.4.1 Non-gallstone-related acute pancreatitis (Paper I–IV)

The outcome of interest in **Paper I–IV** was incident non-gallstone-related acute pancreatitis. The reason why I only studied one subtype of the disease was to avoid analyses of acute pancreatitis as a proxy for symptomatic gallstone disease. A number of studies have already observed associations between diet and

[33]Made possible via the personal identity number, a unique number that identifies every Swedish citizen.
[34]PPV is the probability that subjects with a positive test (a recorded ICD-10 code) truly have the disease (using a "gold standard", which, in this case, was their medical records).

risk of cholecystectomy (used as a proxy for symptomatic gallstone disease) (Leitzmann et al., 2002; Leitzmann, Willett, et al., 1999; Nordenvall et al., 2015, 2016; Tsai et al., 2005a, 2005b, 2006)—that is to say, the same surgical procedure that is recommended by current international guidelines as the definitive treatment for all patients with gallstone-related acute pancreatitis (Tenner et al., 2013; UK Working Party on Acute Pancreatitis, 2005; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). (Table S.1 in the Supplementary material gives some evidence for gallstone-related acute pancreatitis and cholecystectomy acting as fairly equal proxies for symptomatic gallstone disease, with each outcome having highly similar associations in terms of direction and magnitude with several risk factors.)

Non-gallstone-related acute pancreatitis was defined as an episode of acute pancreatitis (except K85.1 [biliary pancreatitis]) for which no diagnosis of cholelithiasis (gallstones) (diagnosis code of K80 in ICD-10) or surgery to the gallbladder and bile duct (surgical code of JKA20 and JKA21 [cholecystectomy], JKE00 [transduodenal papillotomy], JKE02 [transduodenal endoscopic incision of common bile duct], JKE12 [endoscopic extraction of calculus from bile duct], JKE18 [endoscopic insertion of stent into bile duct], or JKB30 [percutaneous transhepatic biliary drainage] in NOMESCO Classification of Surgical Procedures)[35] was recorded within 3 months after the index episode. In total, 56% (n = 502) (62% in men [n = 326] and 48% in women [n = 176]) of all episodes of acute pancreatitis were classified as non-gallstone-related acute pancreatitis according to this definition, which was similar to that in Swedish studies with access to medical charts (52 to 61%) (Bertilsson et al., 2015; Lindkvist et al., 2012; Razavi et al., 2011). Figure 3.3 shows the 2-year classification percentage of non-gallstone-related acute pancreatitis during the follow-up period (1998 to 2014).

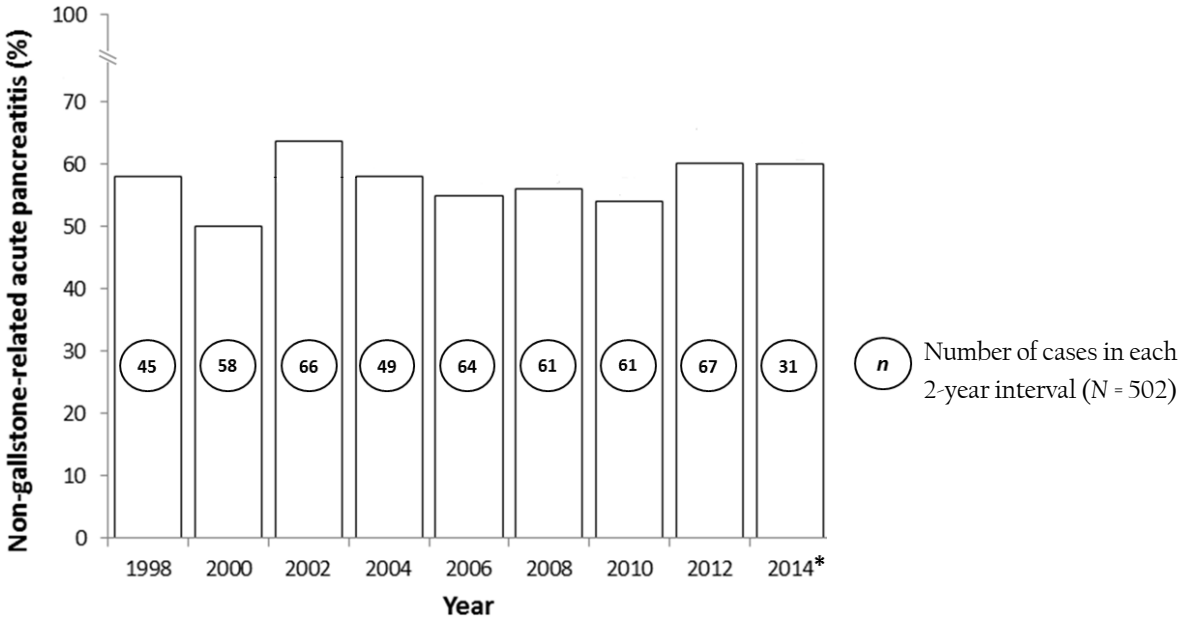

Figure 3.3: Percentage (height of bar) of all incident episodes of acute pancreatitis that were classified as non-gallstone-related acute pancreatitis in the study cohorts, 1998 to 2014, according to 2-year intervals.
*Only represents 1 year (2014).

[35] *Transduodenal*, passing across or through the duodenum; *papillotomy*, incision of the duodenal papilla; *percutaneous*, passing through the skin; and *transhepatic*, passing through the bile ducts.

3.4.2 Recurrent and progressive pancreatic disease (Paper V)

The outcome of interest in **Paper V** was recurrent (acute pancreatitis) and progressive pancreatic disease (chronic pancreatitis or pancreatic cancer) among individuals who had had an incident episode of non-gallstone-related acute pancreatitis (see section 3.4 for specific ICD-10 codes of each outcome). Since the validation study of the SNPR was restricted to incident episodes of acute pancreatitis (R. Ljung, personal communication, 21 February, 2014; Razavi et al., 2011), I only used primary diagnosis codes for specificity[36] reasons. In addition, because I had an interest in recurrence and progression of non-gallstone-related acute pancreatitis and not in readmission thereof (Vipperla et al., 2014; Whitlock et al., 2010), all pancreatitis-related hospital care that occurred within 90 days of the diagnosis was considered to be part of the incident episode. Among 400 individuals with non-gallstone-related acute pancreatitis, in whom the incident episode was diagnosed between 1998 and 2013, and who were alive at 90 days after the diagnosis and had subsequent follow-up until the end of 2014, a total of 91 cases of recurrent and progressive pancreatic disease were recorded (60 in men and 31 in women). Of these, 77 had recurrent acute pancreatitis, 11 had non-malignant chronic disease, and 3 had cancer. Even though the overall rate of recurrent and progressive pancreatic disease (5 cases per 100 persons and year) was identical to that in a large, regional study from Malmö and Lund (in which 1457 patients were recruited and followed up between 2003 and 2013) (Bertilsson et al., 2015), it was lower in a relative comparison because the study population in **Paper V** was restricted to cases of non-gallstone-related acute pancreatitis (ie, the subtype with the highest risk of recurrent and progressive pancreatic disease [Yadav and Lowenfels, 2013]). There are several potential reasons for why the risk was (relatively) lower in my data (all of which have been discussed in detail in the Discussion section of **Paper V**) but could, in principle, be explained by the fact that the other study did not use a 90-day post-diagnosis window. (Although not further discussed after this subsection, it might be worth to highlight that the risk of recurrent episodes of acute pancreatitis was less than 9% among those with gallstone-related acute pancreatitis, which was highly similar to that observed in other studies when the recommendations for cholecystectomy are being followed [see references in subsection 1.2.3]—providing further evidence that the definition used to classify subtypes of acute pancreatitis in this thesis was fairly correct.)

[36] Specificity is the probability of a negative test given that the disease is absent. Thus, a high specificity avoids false-positive cases.

3.5 Analytical cohorts and follow-up periods

The analytical cohort sizes and follow-up periods of **Paper I–V** are shown in Figure 3.4. In all of the studies, the questionnaire responders were excluded if their personal identity numbers were incorrect, if they had turned in a blank questionnaire, or if they, at baseline, which was set at January 1, 1998, had died, had a history of cancer (apart from non-melanoma skin cancer) or pancreatic disease, or had reported an implausible energy intake (indicating a high degree of misreporting; defined as >3 standard deviations [SDs] of the sex-specific log-transformed mean value).[37] The exclusion of those with cancer, a standard procedure in epidemiology, was to reduce the influence of post-diagnosis changes in diet and lifestyle habits. Details on the study-specific exclusion criterions for the studies on incidence (blue connectors and boxes in Figure 3.4) and the study on recurrence and progression (red connectors and boxes in Figure 3.4) are given below.

3.5.1 Incidence studies (Paper I–IV)

In **Paper I**, which had a follow-up period of 12 years (1998 to 2009), further exclusions were made of participants who, at baseline, had missing information on total vegetable consumption or on total fruit consumption as well as of those who, during follow-up, had developed pancreatic cancer. The rationale for the latter exclusion was to minimize between-disease misclassification, since symptoms that lead to a diagnosis of acute pancreatitis may be due to an underlying malignancy (Dzeletovic et al., 2014).

In **Paper II**, for which the follow-up period lasted from 1998 to 2010 (13 years), participants who had developed pancreatic cancer during follow-up were further excluded.

In **Paper III**, which also had a follow-up period of 13 years (1998 to 2010), further exclusions were made of participants who, at baseline, had missing information on fish consumption (either on lean fish or on fatty fish) or had reported an extremely high fish consumption (>7.0 servings/week). The latter exclusion was chosen a priori, because I considered consumption at that level to be unlikely high (the 95th percentile, that is, the value at which 95% of the study population had their consumption, was 4.5 servings/week).[38] In addition, those who had developed pancreatic cancer during follow-up were excluded.

In **Paper IV**, for which the follow-up period lasted from 1998 to 2012 (15 years), participants who had missing or extremely high coffee consumption at baseline were further excluded (>10 cups/day) (95th percentile: 7 cups/day), as were those who had developed pancreatic cancer during follow-up.

3.5.2 Recurrence and progression study (Paper V)

In **Paper V**, which included participants who had been diagnosed with acute pancreatitis between 1998 and 2013, and for whom post-diagnosis follow-up was available until 2014, everyone who had not received a diagnosis of acute pancreatitis during the recruitment period was excluded. In addition, the

[37] In the individual studies, the criterions "turned in a blank questionnaire" and "had died" were not mentioned by name for reasons of space.

[38] Since this can been seen as a rather arbitrary cut-off value, I changed it to >14.0 servings/week in a secondary analysis, which, however, had no influence on the study results.

following exclusion criterions were applied: (*i*) history of pre-diagnosis chronic pancreatic disease (including cancer), (*ii*) evidence of such chronic pancreatic diseases and/or gallstone-related acute pancreatitis at the end of the aforementioned 90-day post-diagnosis window, and (*iii*) non-completion of the 90-day post-diagnosis window (due to death or end of the recruitment period). (See section 3.4 for definitions and specific ICD-10 codes of each criterion.) The reason for these exclusions was to obtain a study population that consisted only of cases of incident non-gallstone-related acute pancreatitis.

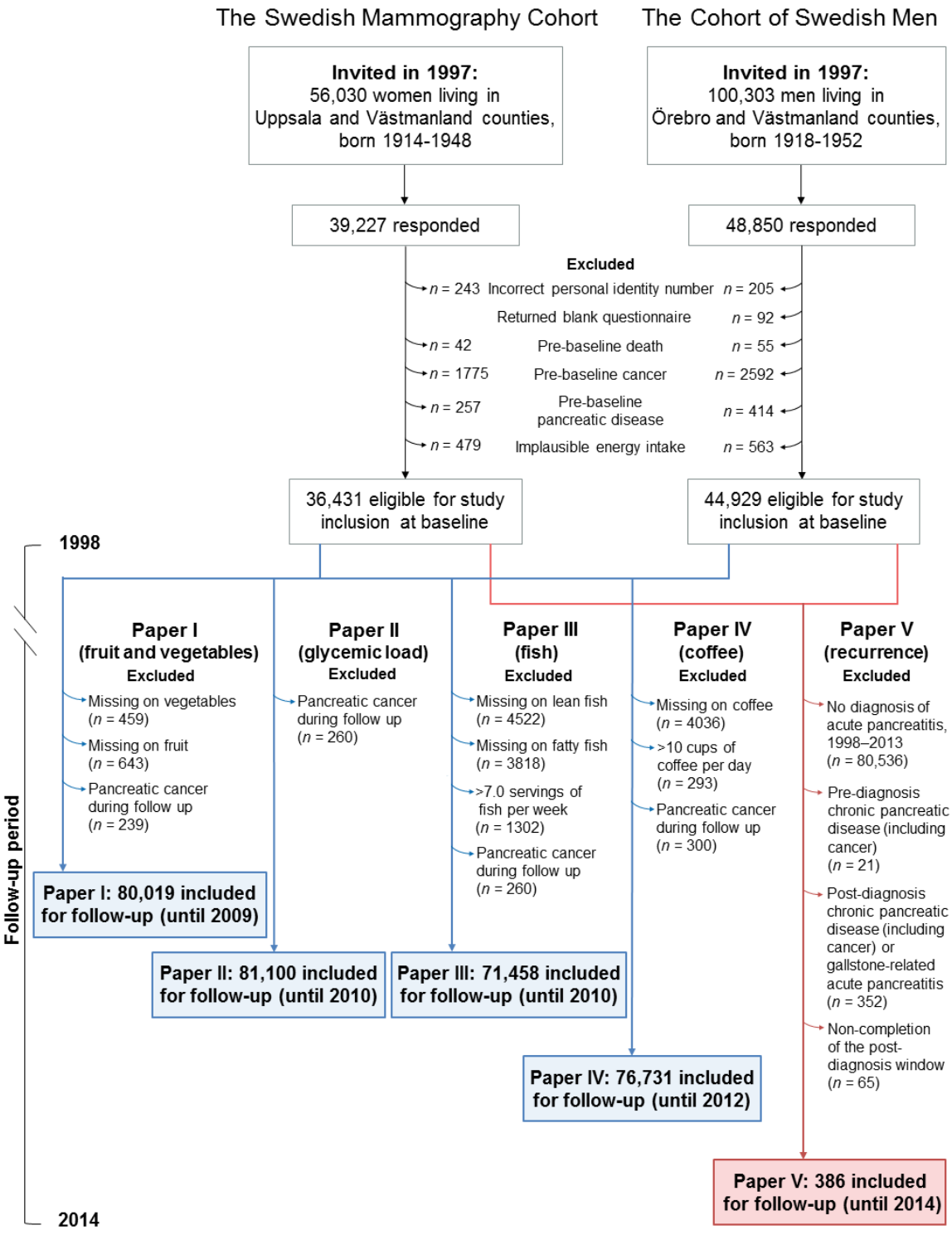

Figure 3.4: Flow chart of **Paper I–V**. Blue connectors and boxes represent the studies on incidence, whereas those of red color represent the study on recurrence and progression. The vertical placement of the blue and red boxes represents the length of follow-up in each study. Modified with permission from Wallin (2016).

3.6 Statistical analyses

Time-to-event analysis, also called survival analysis, is the branch of statistics that was used to examine the association between diet and risk of non-gallstone-related acute pancreatitis. It refers to the time interval between a specific point in time, say, the completion of a questionnaire, to the occurrence of a well-defined event,[39] say, an episode of acute pancreatitis (Tolles & Lewis, 2016). Two ways to describe the distribution of survival time are the survival function and the hazard function, of which only the latter will be discussed in this thesis. As noted by Hernán (2010), the hazard function can "for all practical purposes… be thought of as [an] incidence [rate]".[40] A distinctive feature of time-to-event data is that there might be individuals for whom the outcome of interest has not occurred at the end of the follow-up period (so-called right-censoring; see Figure 3.5, left panel, for a schematic overview) and there is no way to know if it will occur in the near future, the distant future, or at all. (For a more "in-depth" overview of survival analysis and its various features, I can warmly recommend 2 recently defended theses from the Unit of Nutritional Epidemiology [Bellavia, 2015; Discacciati, 2015].)

In **Paper I–IV**, the participants accrued follow-up time from the start of follow-up (January 1, 1998) to the date of diagnosis of acute pancreatitis, date of diagnosis of chronic pancreatic diseases, date of death, or end of follow-up (December 31, 2009 [**Paper I**], December 31, 2010 [**Paper II–III**], or December 31, 2012 [**Paper IV**]), whichever came first. In **Paper V**, the start of follow-up was set to 90 days after the incident episode of non-gallstone-related acute pancreatitis, and the participants accrued follow-up time until the date of recurrent acute pancreatitis, date of progression to other pancreatic diseases (including cancer), date of death, or December 31, 2014 (end of follow-up), whichever came first.

3.6.1 Cox regression

Cox regression—the choice of analytical method in this thesis—is widely used for analysis of time-to-event data and has been so during the last decades (Cox, 1972).[41] It estimates hazard ratios (HRs), which, roughly, can be interpreted as the multiplicative extent to which an exposure increases or decreases an incidence rate (Hernán, 2010). In the forthcoming subsections, I will discuss 2 important and general aspects of Cox regression (ie, time scale and proportional hazards assumption), followed by thesis-specific aspects (ie, modeling of exposures and covariates, sensitivity analyses, and subgroup analyses). Also, for those readers who are more statistically oriented, the formal equation of the Cox regression model is given below for (*i*) the hazard function ($h[t|\mathbf{x}_j]$) for one subject (denoted "j") as a function of exposure $\mathbf{x}_j$ and (*ii*) the hazard ratio (HR) comparing that subject with another subject (denoted "m").

$$(i)\ h(t|\boldsymbol{x_j}) = h_0(t)\exp(\boldsymbol{x_j\beta_x}) \qquad (ii)\ HR = \frac{h(t|\boldsymbol{x_j})}{h(t|\boldsymbol{x_m})} = \frac{\exp(\boldsymbol{x_j\beta_x})}{\exp(\boldsymbol{x_m\beta_x})}$$

[39] The terms *event*, *outcome*, and *disease* are equivalent and are, therefore, used interchangeably in this thesis.
[40] More formally, the hazard function is defined as the "probability that the event occurs in [an infinitively small] time interval, given that the subject has survived to the beginning of the interval, divided by the time interval" (Bellavia, 2015).
[41] Other analytical methods are accelerated failure time models and Royston-Parmar models.

3.6.1.1 Time scale

Historically, the most common time scale in Cox regression models has been the time-on-study time scale, defined as the time interval between the date of study entry and the date of study exit (due to disease occurrence and/or right-censoring) (Figure 3.5, left). However, it is becoming increasingly common to use attained age as the time scale (Cologne et al., 2012; Thiébaut & Bénichou, 2004) (Figure 3.5, right). Instead of entering the study at a fixed point in time, the participants are assumed to enter at their age at baseline and to exit at their age at disease occurrence and/or right-censoring. A great advantage with attained age as the time scale is that it directly controls for changes in the hazard function associated with changes in age (which is a very strong risk factor for most diseases), without needing to incorporate age as a separate covariate or to model it in a specific way.

The primary time scale used in the main analyses of **Paper I**, **III**, and **IV** was time-on-study, whereas it was attained age in the main analyses of **Paper II** and **V**.

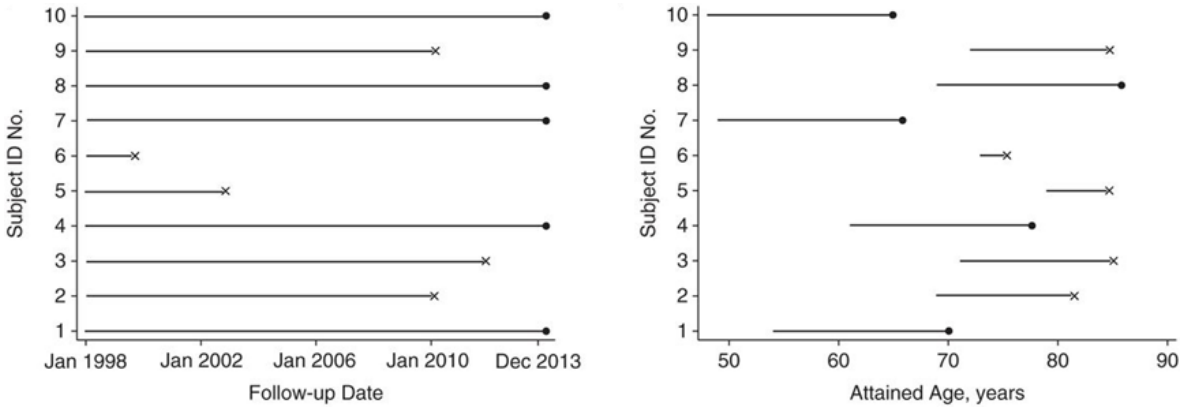

Figure 3.5: Example of time-on-study (left) and attained age (right) as the time scale in a Cox regression model. Crosses represent cases and dots represent right-censored observations. Modified from Bellavia, Discacciati, Bottai, Wolk, & Orsini (2015) with permission of Oxford University Press.

3.6.1.2 Proportional hazards assumption

The Cox regression model is a proportional hazards model, which, simply put, means that it assumes that the HRs are *proportional over time* or, even more simply put, that the HRs are the same at any point in time during the follow-up period (or at any value of age, if that is the time scale) (Bellavia, 2015; Discacciati, 2015). An example of proportional hazards is shown in the left panel of Figure 3.6, whereas an example of non-proportional hazards is shown in its right panel. The presentation of a single, average (time-fixed) Cox regression-derived HR of 0.94 is appropriate in the left scenario, but it is less so with a single, time-fixed Cox regression-derived HR of 0.89 in the right scenario (clearly, the HRs are much lower than that for younger ages). Therefore, to interpret the data correctly, it is important to test the assumption of proportional hazards in a Cox regression model and, if there is evidence of such a violation, to handle it appropriately. (For technical and practical details on how to evaluate and handle non-proportional hazards in Cox regression, which is beyond the scope of this thesis, please see Royston & Lambert [2011] and Oskarsson [2015] [both references are based on the statistical software Stata].)

In this thesis, the proportional hazards assumption was tested by using the Schoenfeld test (**Paper I**, **II**, and **IV**) (Schoenfeld, 1980) and by modeling interactions[42] between linear (**Paper III** and **V**) and flexible (**Paper V**) functions of analysis time and the exposures of interest (Discacciati, Oskarsson, & Orsini, 2015). However, there was no formal evidence of departure from the assumption of proportional hazards for the main exposure(s) in **Paper I–V**.

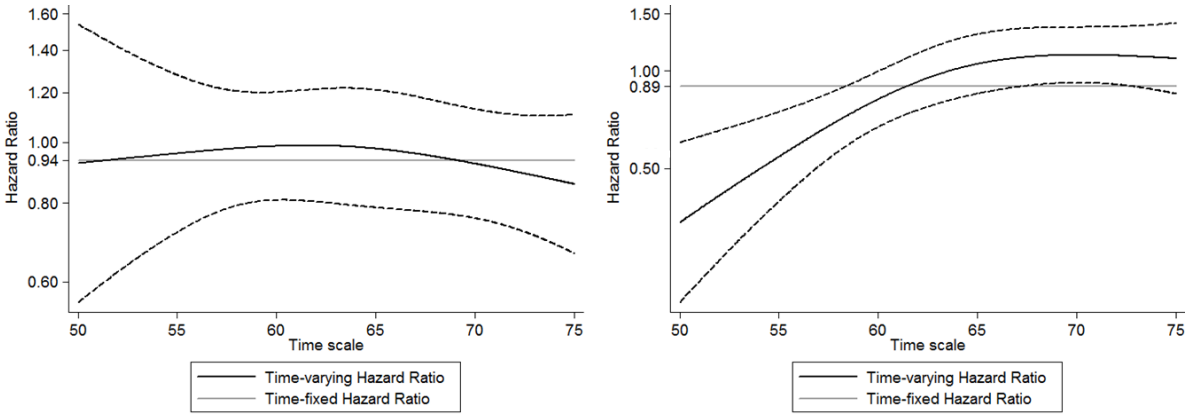

Figure 3.6: Examples of proportional hazards (left) and non-proportional hazards (right). The gray line represents the time-fixed HR that was derived from a standard Cox regression model and the black lines represent the time-varying HRs and 95% confidence intervals that were obtained from a Cox regression model in which the HRs were allowed to vary over the time scale (attained age). The HRs vary considerably across attained age in the right scenario, thereby indicating a violation of the proportional hazards assumption. The figures were produced by using the post-estimation command stphcoxrcs in Stata (Discacciati et al., 2015). Data were obtained from Nordenvall et al. (2016).

3.6.1.3 Modeling of exposures and covariates

In **Paper I**, the variables for fruit consumption and vegetable consumption were modeled in a continuous (using linear and spline functions) and a categorical (according to quintiles[43]) fashion. In the multivariable model, in which fruit and vegetables were included simultaneously, the following covariates[44] were adjusted for: age, sex, education, cigarette smoking, alcohol intake, BMI, history of diabetes, and energy intake (see **Paper I** for the modeling of each covariate). Inevitably, there will always be missing data in epidemiological studies, especially in very large cohort studies with thousands of participants, which, in one way or another, must be accounted for. As detailed in section 3.5, the participants who had missing data on the main exposure(s) in **Paper I–IV** were excluded. Missing data on covariates (a total of 7% in the multivariable model of **Paper I**) were handled using the missing-indicator method in **Paper I–IV**, in which an extra category (an indicator) is added to represent the missing data of each covariate (Knol et al., 2010).

[42]The term *interaction* (also known as *effect modification*) refers to the situation in which an exposure-outcome association differs by levels of another factor (in this case: the time scale).
[43]One quintile represents one-fifth of a population; one quartile represents one-fourth of a population; and one tertile represents one-third of a population.
[44]I define a covariate as a secondary variable that can either distort (a confounding variable), mediate (an intermediate variable), or modify (an interaction variable) an exposure-outcome association. The concepts of confounding, mediation, and interaction will be further discussed in later subsections and chapters.

In **Paper II**, the variable for glycemic load was modeled continuously (using linear and spline functions) and categorically (according to quartiles) in separate exposure models. The secondary exposures, that is, glycemic index and carbohydrate intake, were modeled as categorical variables (according to quartiles). The multivariable model included age, sex, cigarette smoking, and alcohol intake (a total of 4% of missing data), although I tried to adjust for several other covariates (see **Paper II** for details of covariates and their modeling).

In **Paper III**, the variable for total fish consumption was modeled as a continuous variable (using linear and spline functions), while those for fatty fish consumption and lean fish consumption were modeled as categorical variables (≤0.5, 0.6–2.0, >2.0 servings/week). The multivariable model was adjusted for age, sex, education, cigarette smoking, alcohol intake, BMI, use of fish oil supplements, vegetable consumption, and history of diabetes and/or hyperlipidemia (a total of 6% of missing data) (even though, once again, several other covariates were considered; see **Paper III** for details of covariates and their modeling). In addition, in the analyses of subtypes of fish, the variables for fatty fish and lean fish were included in the same multivariable model.

In **Paper IV**, the variable for coffee consumption was modeled in a continuous (using linear and spline functions) and a categorical (<2, 2, 3–4, ≥5 cups/day) fashion. Included in the multivariable model were age, sex, education, cigarette smoking, alcohol intake, and physical activity (12% of missing data in total) (see **Paper IV** for details of covariates and their modeling, including those considered but not included).

In **Paper V**, the variable for the RFS was modeled as a continuous variable (using linear and spline functions) and also as a categorical variable (according to approximate tertiles). Multivariable models were adjusted for age, sex, education, cigarette smoking, alcohol intake, BMI, physical activity, history of diabetes and/or hyperlipidemia, the non-RFS, and energy intake (all assessed at baseline) as well as for length of hospital stay (used as a proxy for disease severity) and calendar year of diagnosis. To avoid a too low number of events per parameter in the Cox regression model, which might lead to systematic errors[45] in HRs and 95% confidence intervals (CIs)[46] (Vittinghoff & McCulloch, 2007), I modeled categorical covariates as binary variables and continuous covariates as linear variables (nota bene, binary variables and linear variables are counted as one-parameter variables) (see **Paper V** for the specific modeling of each covariate). For the same reason, and in contrast to **Paper I–IV**, multiple imputation by chained equations was used to handle missing data, including that on the main exposure (White, Royston, & Wood, 2011). This is a statistical technique in which missing values are replaced (imputed) by predicted values from a multivariable regression model. By creating multiple data sets, as opposed to a single or a few data sets, the variability of the imputed values can be accounted for. The overall percentage of missing data was 19% and I created a total of 40 imputed data sets. The HRs from all data sets were combined using the so-called Rubin's rule, which accounts for variations between and within data sets.

[45]Also known by the term *bias*. Different sources of bias, and their potential implication on the results of this thesis, will be discussed in detail in later chapters.
[46]A 95% CI is a range of values for which one can be 95% certain that the true value of the population lays.

As mentioned in the previous paragraphs, I used both linear and spline functions (more specifically, cubic spline functions [order of 3]) to model continuous variables (Orsini & Greenland, 2011). The assumption of a linear exposure-outcome association is common, intuitive, and leads to results that are easy to interpret (ie, a constant change in risk for each unit of change in the exposure), but there is no reason to believe that this assumption holds in all situations, especially if it has not been tested for. The use of cubic splines is a way to relax the linearity assumption, thereby allowing for non-linear exposure-outcome associations.[47] The simplest, but perhaps not the most technically correct, analogy of cubic splines is to view them as pieces of a broken stick. Each piece is allowed to have its own, separate shape (a cubic function) and the pieces are then joined together at so-called knots. The result is a continuous curve that is smoothed at the knot boundaries (Figure 3.7). If such a curve is constrained to be linear before the first knot, and/or after the final knot, it is known as a restricted cubic spline. This constraint is to avoid instability at the tails of a covariate's distribution. In **Paper I–V**, both-tail restricted cubic splines with 3 knots at fixed percentiles (10th, 50th, and 90th) of the exposure distribution were used.

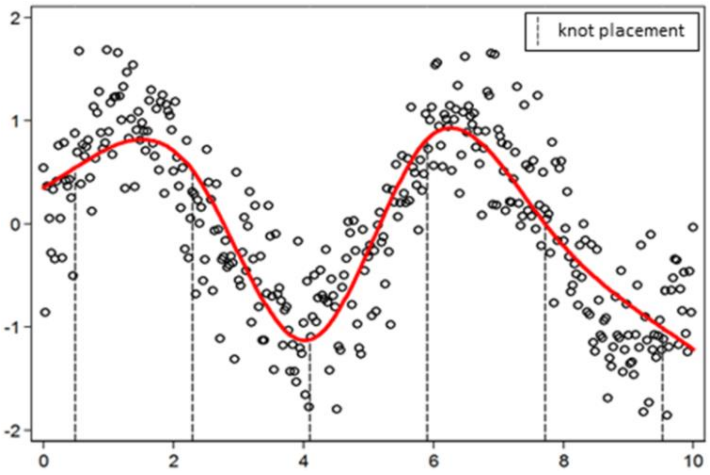

Figure 3.7: Example of a continuous variable that is modeled using cubic splines. The dashed vertical lines indicate the knot placement, with the horizontal distance between the lines being equal to the width of the cubic splines.

3.6.1.4 Sensitivity analyses

A number of sensitivity analyses were performed in **Paper I–IV**, with the aim of examining how robust the results of the main analyses were (see **Paper I–IV** for details). In this thesis, I have chosen to highlight the sensitivity analyses that are listed in Table 3.3; the results of which may, or may not, have already been presented in the individual studies. Similarly, of all the sensitivity analyses that were performed in **Paper V**, I will only focus on that which examined changes in dietary intake, cigarette smoking, and alcohol drinking following a diagnosis of non-gallstone-related acute pancreatitis. To do so, the questionnaire data from 1997 were compared with that from 2009.

3.6.1.5 Subgroup analyses

A number of subgroup analyses were also performed in **Paper I–IV**, with the aim of examining whether the results of the main analyses differed by levels of other variables (so-called effect modification or interaction) (see **Paper I–IV** for details). More specifically, the aim was to assess biological interaction

[47]Other ways are by using fractional polynomials or by categorizing a continuous variable.

(which refers to aspects and understanding of biological mechanisms) rather than statistical interaction (which refers to aspects and improvements of data fitting) (Ahlbom & Alfredsson, 2005; Rothman, 2012). I have chosen to highlight the subgroup analyses by alcohol intake in this thesis, which will be "standardized" so that the results for each main exposure (modeled as a continuous variable) are presented according to strata of low and high alcohol intake (defined as 12 g or more per day).[48] Subgroup analyses were not considered meaningful in **Paper V** because of the low number of cases of recurrent and progressive pancreatic disease.

Table 3.3: Sensitivity analyses of **Paper I–IV**

Sensitivity analysis	Purpose
Adjusting for a joint multivariable model*	To account for differences in the choice of covariates and their modeling
Excluding potential intermediate factors†	To account for factors that may mediate an exposure-outcome association
Using attained age as time scale	To account for differences in the choice of time scale
Using multiple imputation for missing data	To account for how the missing data were handled
Excluding the first 2 years of the follow-up	To account for exposure changes due to pre-clinical or chronic illnesses
Applying a stricter outcome definition‡	To account for misclassification of the outcome (due to underdetection of gallstones [Johnson & Lévy, 2010])

*Age, sex, education (≤12, >12 years), cigarette smoking (never smoker, past smoker with <10 or ≥10 pack-years, current smoker with <20 or ≥20 pack-years), alcohol intake (sex-specific quartiles of g/day), body mass index (<25, 25–29, ≥30 kg/m^2), physical activity (<20, 20–40, >40 min/day), history of diabetes (yes, no) and hyperlipidemia (yes, no), energy intake (sex-specific quartiles of kcal/day), fruit consumption (quintiles of servings/day), vegetable consumption (quintiles of servings/day), glycemic load (quartiles of score/day), total fish consumption (<1.0, 1.0–1.9, 2.0–3.0, >3.0 servings/week), and coffee consumption (<2, 2, 3–4, ≥5 cups/day).
†Fruit and vegetable consumption (Appleton et al., 2016; Carter et al., 2010; Yuan, Lee, Shin, Stampfer, & Cho, 2015), high-glycemic load diets (Bhupathiraju et al., 2014; Levitan et al., 2008; Murakami, McCaffrey, & Livingstone, 2013), fish consumption (Eslick, Howe, Smith, Priest, & Bensoussan, 2009; Gunnarsdottir et al., 2008), and coffee consumption (O'Keefe et al., 2013; Rebello & van Dam, 2013) might affect the occurrence of obesity/adiposity, diabetes, and hypertriglyceridemia—that is, potential risk factors for acute pancreatitis (as summarized in Table 1.1).
‡No history of cholelithiasis and/or gallbladder and bile duct surgeries within 3 years after the index episode (or for as long as there were post-diagnosis follow-up data if the follow-up was less than 3 years) of non-gallstone-related acute pancreatitis.

3.6.2 Statistical software

All statistical analyses were run in Stata version 12 (StataCorp), with statistical significance set at a 2-sided *P* value of less than 0.05.[49] *P* values have to be interpreted in the context of hypothesis testing; for example, in **Paper II**, I tested the null hypothesis that "high-glycemic load diets *have no effect* on the incidence of non-gallstone-related acute pancreatitis". *P* values represent the probability to obtain the observed (or a more extreme) difference if the null hypothesis is true. Values close to 0 indicate that the observed results are unlikely to be consistent with chance alone, meaning that the null hypothesis can be rejected and an alternative hypothesis can be accepted ("high-glycemic load diets *have an effect*… ")—whereas values close to 1 suggest that the observed results are highly compatible with the null hypothesis. In general, a 1:1 relation exists between a 2-sided *P* value and a 95% CI in the sense that if the CI does not include 1 (or 0, if absolute differences are calculated), the *P* value is less than 0.05.

[48]I would like to stress that I consider analyses by sex to be an extension of the main analyses rather than a subgroup analysis, and, therefore, I will present results by sex together with the main results of **Paper I–IV**.
[49]The choice of 0.05 as a threshold for statistical significance is arbitrary (but accepted as a standard by the research community). Why a *P* value of 0.048 would be more "significant" than one of 0.055 is hard to understand from an intellectual perspective, yet a study with the former *P* value often receives way more praise.

4 Results

In this chapter, the major results of **Paper I–V** will be outlined. I will first present the main (and secondary) results of the studies on the association between diet and incidence of non-gallstone-related acute pancreatitis (**Paper I–IV**), followed by those of the study on the association between diet and risk of recurrent and progressive pancreatic disease (**Paper V**). (For the full results, I refer the reader to the Results section of **Paper I–V**. Of particular interest might be **Table I**, **Paper V**, which details the overall distribution of non-dietary characteristics of [*i*] everyone who were eligible for study inclusion in **Paper I–V** and [*ii*] those who developed non-gallstone-related acute pancreatitis between 1998 and 2013.)

4.1 Incidence studies (Paper I–IV)

4.1.1 Main results

4.1.1.1 Fruit and vegetables (Paper I)

There were 44,103 men and 35,916 women included in the study, who contributed 891,136 person-years of follow-up[50] and 320 cases of non-gallstone-related acute pancreatitis between 1998 and 2009. At baseline, the mean consumption of vegetables was 2.6 servings/day and that of fruit was 1.7 servings/day. Baseline characteristics by fruit consumption and vegetable consumption are shown in **Table I**, **Paper I**.

I observed a statistically significant inverse association between vegetable consumption and risk of non-gallstone-related acute pancreatitis (*P* for overall association = 0.01)[51] (Figure 4.1, left). After adjustment for potential confounders, that is, the covariates that might obscure a true association and/or produce a spurious one, the HR was 0.56 (95% CI, 0.37–0.84) for the highest compared with the lowest quintile of vegetable consumption.[52] Each 2 additional servings of vegetables per day were associated with a HR of 0.83 (95% CI, 0.70–0.98) in the continuous analysis (**Figure I**, **Paper I**), and I found no evidence to reject the null hypothesis of linearity in the restricted cubic spline model (*P* for non-linearity = 0.18).[53] Separate analyses of men (HR, 0.83; 95% CI, 0.67–1.03) and women (HR, 0.85; 95% CI, 0.66–1.11) showed highly similar results. In contrast, I observed no statistically significant association between fruit consumption and risk of non-gallstone-related acute pancreatitis (*P* for overall association = 0.43) (Figure 4.1, right); the HR for the highest compared with the lowest quintile was 1.20 (95% CI, 0.81–1.78) and that for every 2 additional servings/day was 1.13 (95% CI, 0.94–1.36) (*P* for non-linearity = 0.81). Results were similar in separate analyses of men and women (HR in the continuous model, 1.15 [95% CI, 0.91–1.46] and 1.12 [95% CI, 0.84–1.50], respectively).

---

[50]Equal to the sum of each individual's time at risk, which, in this study, could range from 1 day to 12 years. One person-year can represent the follow-up of 1 person for 1 year, 2 persons for 6 months, or 12 persons for 1 month.
[51]A test for overall association is testing the null hypothesis that a variable as a whole (and not just parts of it) *has no association* with an outcome. The tests that I used for this purpose are outlined in Figure 4.1 to 4.5.
[52]This finding can be interpreted as a 44% (1-0.56) lower incidence rate (or more formally, hazard function) in the one-fifth of participants who ate the most vegetables compared with the one-fifth who ate the least. It does not, however, at least not by default, imply that a low vegetable consumption is a direct cause of the disease.
[53]When a both-tailed, 3-knot restricted cubic spline is used, a test for non-linearity is conducted by testing the coefficient of the second spline transformation equal to zero.

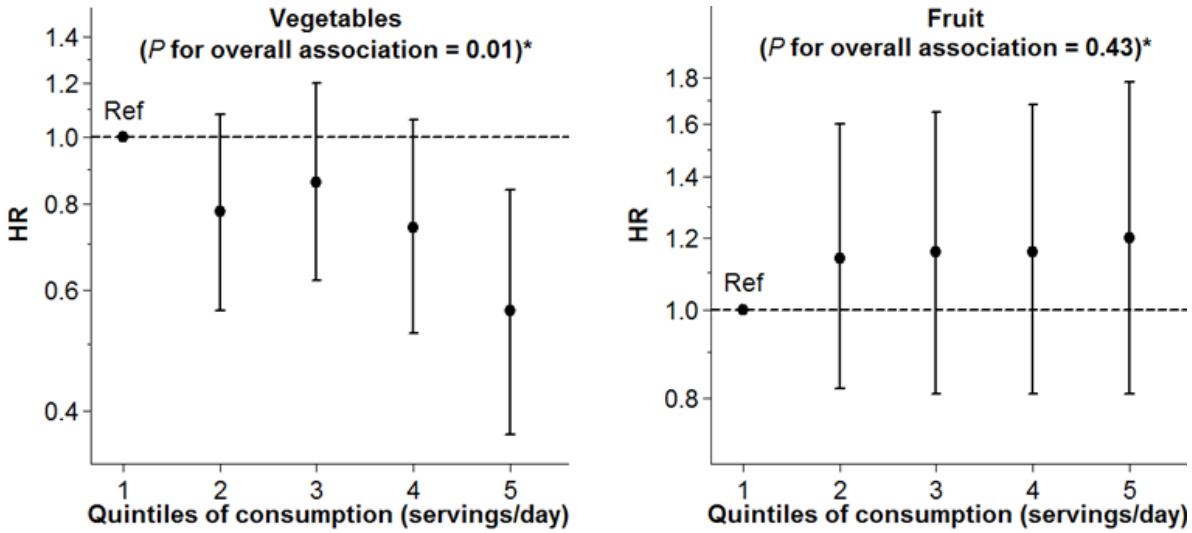

Figure 4.1: Multivariable-adjusted HRs and 95% CIs of non-gallstone-related acute pancreatitis by quintiles of vegetable consumption (left) and fruit consumption (right).
*Test for overall association was conducted by assigning the median (50th percentile) value to each quintile and then entering these values as a continuous variable in the Cox regression model.

4.1.1.2 Glycemic load (Paper II)

Included in the study were 44,791 men and 36,309 women, who contributed 967,568 person-years of follow-up and 364 cases of non-gallstone-related acute pancreatitis between 1998 and 2010. At baseline, the mean daily score of glycemic load was 191. Baseline characteristics by sex and glycemic load are shown in **Table I**, **Paper II**.

I observed a statistically significant positive association between glycemic load and risk of non-gallstone-related acute pancreatitis (*P* for overall association < 0.01) (Figure 4.2, left). After adjustment for potential confounders, the HR was 1.60 (95% CI, 1.17–2.18) for the highest compared with the lowest quartile of glycemic load. In the restricted cubic spline model, there was no evidence of a non-linear association (*P* for non-linearity = 0.74) (**Figure I, Paper II**). Each 50 units increase in glycemic load per day (corresponding to around 3 servings of white bread [Foster-Powell et al., 2002]) were associated with a HR of 1.38 in both sexes combined (95% CI, 1.15–1.65) as well as in men (95% CI, 1.11–1.72) and women (95% CI, 1.02–1.86) separately. Similar exposure-outcome associations (in comparison with each other) were seen for the 2 variables that constitute glycemic load (Figure 4.2, right); although, if anything, the association appeared to be slightly stronger for the quantitative aspect (carbohydrate intake, *P* for overall association = 0.01) than for the qualitative aspect (glycemic index, *P* for overall association = 0.02).

4.1.1.3 Fish (Paper III)

There were 39,267 men and 32,191 women included in the study, who contributed 860,176 person-years of follow-up and 320 cases of non-gallstone-related acute pancreatitis between 1998 and 2010. A mean of 1.9 weekly servings of fish were consumed at baseline. **Table I**, **Paper III** gives baseline characteristics by sex and total fish consumption.

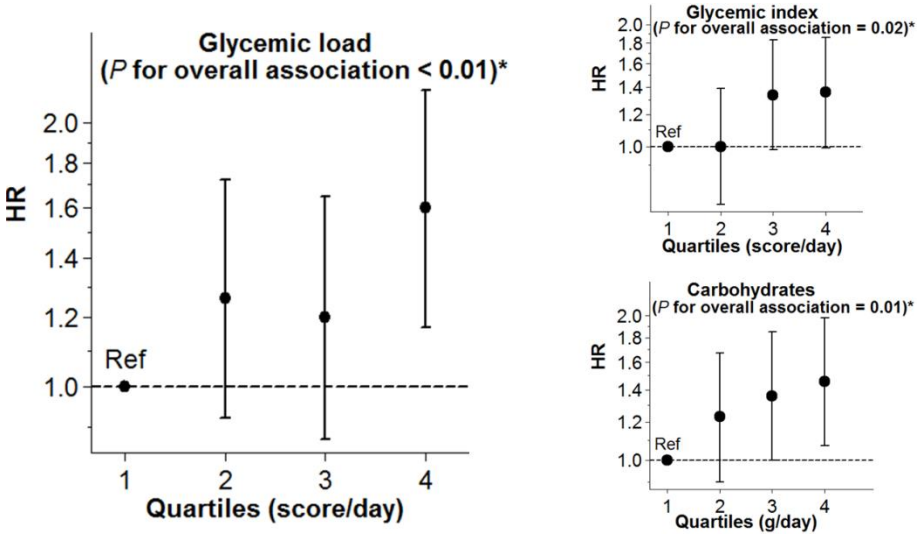

Figure 4.2: Multivariable-adjusted HRs and 95% CIs of non-gallstone-related acute pancreatitis by quartiles of glycemic load (left), glycemic index (upper right), and carbohydrate intake (lower right).
*Test for overall association was conducted by assigning the median value to each quartile and then entering these values as a continuous variable in the Cox regression model.

I observed a statistically significant inverse association between total fish consumption and risk of non-gallstone-related acute pancreatitis (*P* for overall association = 0.04) (Figure 4.3, left), which, however, was non-linear in its shape and had an apparent plateau at 2.0–3.0 servings/week (*P* for non-linearity = 0.02) (**Figure I, Paper III**). After adjustment for potential confounders, the HR was 0.77 (95% CI, 0.62–0.96) for 2.4 servings/week compared with 0.9 servings/week (0.74 in men [95% CI, 0.57–0.97] and 0.81 in women [95% CI, 0.55–1.20]). In the analysis of fatty fish and lean fish, I observed that consumption of each subtype had a similarly shaped exposure-outcome association as that for total fish consumption, although neither was statistically significant (*P* for overall association ≥ 0.27) (Figure 4.3, right).

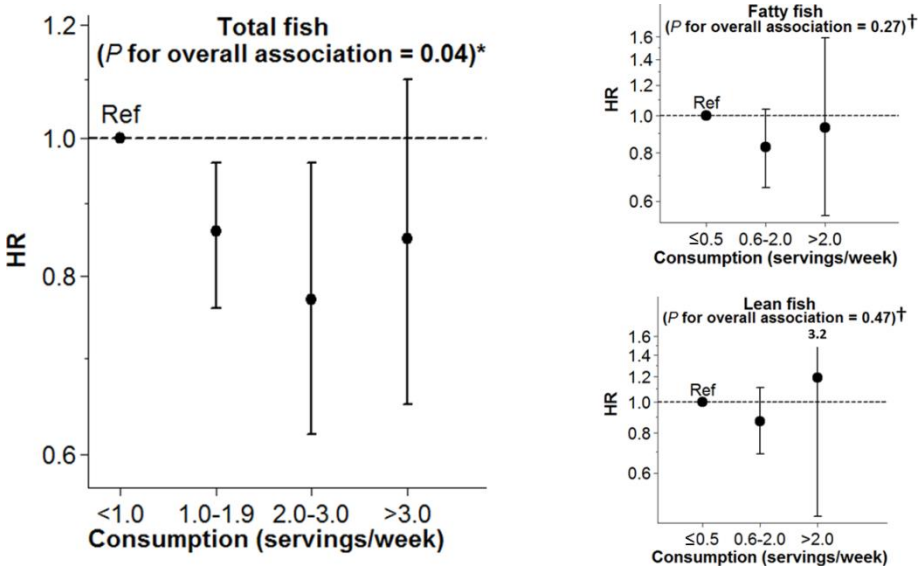

Figure 4.3: Multivariable-adjusted HRs and 95% CIs of non-gallstone-related acute pancreatitis by consumption of total fish (left), fatty fish (upper right), and lean fish (lower right). Total fish consumption were modeled using restricted cubic splines, with HRs calculated according to median values (0.9 [ref], 1.4, 2.4, and 3.5 servings/week).
*Test for overall association was conducted by testing coefficients of spline transformations jointly equal to zero.
†Test for overall association was conducted by testing coefficients of categorical variables jointly equal to zero.

4.1.1.4 Coffee (Paper IV)

Included in the study were 42,215 men and 34,516 women, who contributed 1,035,881 person-years of follow-up and 383 cases of non-gallstone-related acute pancreatitis between 1998 and 2012. At baseline, the mean coffee consumption was 3.3 cups/day. **Table I**, **Paper IV** gives baseline characteristics by sex and coffee consumption.

I observed no statistically significant association between coffee consumption and risk of non-gallstone-related acute pancreatitis (*P* for overall association = 0.34) (Figure 4.4). After adjustment for potential confounders, the HR was 0.84 (95% CI, 0.59–1.20) for 5 or more cups/day compared with less than 2 cups/day. In the restricted cubic spline model, there was no evidence of a non-linear association (*P* for non-linearity = 0.28). Each 1 additional cup of coffee per day was associated with a HR of 0.97 (95% CI 0.92–1.03). Separate analyses of men (HR, 0.99; 95% CI, 0.93–1.06) and women (HR, 0.92; 95% CI, 0.83–1.03) showed fairly similar results.

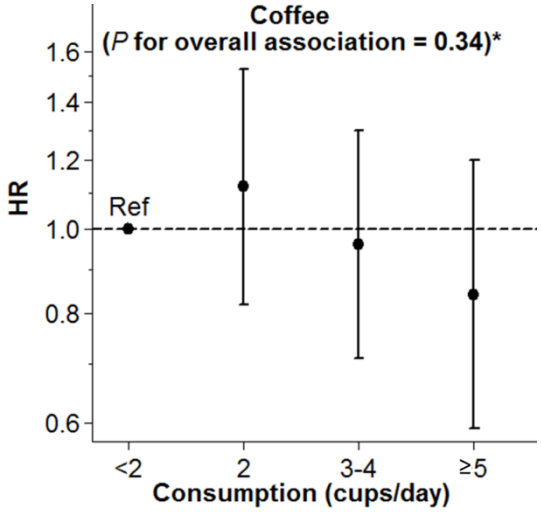

Figure 4.4: Multivariable-adjusted HRs and 95% CIs of non-gallstone-related acute pancreatitis by categories of coffee consumption.
*Test for overall association was conducted by testing coefficients of categorical variables jointly equal to zero.

4.1.2 Sensitivity analysis

The results of the sensitivity analyses in **Paper I–IV** are shown in Table 4.1. Overall, they were very similar to those of the main analyses, with absolute differences in HRs ranging from −0.08 to +0.09 in **Paper I**, from −0.08 to +0.13 in **Paper II**, from −0.03 to +0.01 in **Paper III**, and from −0.01 to +0.03 in **Paper IV**.

Table 4.1: Multivariable-adjusted HRs in the 6 different sensitivity analyses of **Paper I–IV***

	Paper I†		Paper II‡	Paper III§	Paper IV¶
Analysis	**Veg**	**Fru**	**GL**	**Total fish**	**Coffee**
Main	**0.56**	1.20	**1.60**	**0.77**	0.84
Sensitivity‖					
Adjusting for a joint multivariable model	**0.65**	1.23	**1.52**	**0.78**	0.83
Excluding potential intermediate factors	**0.55**	1.19	—	**0.77**	—
Using attained age as time scale	**0.57**	1.17	—	**0.76**	0.85
Using multiple imputation for missing data	**0.55**	1.20	**1.60**	**0.77**	0.84
Excluding the first 2 years of the follow-up	**0.57**	1.16	**1.58**	**0.74**	0.87
Applying a stricter outcome definition	**0.57**	1.12	**1.73**	**0.78**	0.86

Fru, fruit; GL, glycemic load; HR, hazard ratio; Veg, vegetables.
*No confidence intervals are presented for reasons of space; however, HRs with bold font had *P* values less than 0.05. An em dash (—) implies that a particular method or analysis was already part of the main analysis.
†HRs for the highest compared with the lowest quintile of consumption.
‡HRs for the highest compared with the lowest quartile of score.
§HRs for 2.4 servings/week compared with 0.9 servings/week.
¶HRs for 5 or more cups/day compared with less than 2 cups/day.
‖A detailed description of each sensitivity analysis and its purpose is given in Table 3.3. Body mass index, history of diabetes, and history of hyperlipidemia were considered to be potential intermediate factors.

4.1.3 Subgroup analysis

The exposure-outcome associations that I observed for vegetable consumption, high-glycemic load diets, and total fish consumption seemed to be more pronounced in participants who drank 1 or more standard drinks of alcohol per day (equal to 12 g or more of pure alcohol) (Table 4.2).[54] The crude incidence rate of non-gallstone-related acute pancreatitis according to levels of alcohol intake ranged from 33.4 to 34.7 cases (low intake) and from 40.3 to 43.1 cases (high intake) per 100,000 person-years in **Paper I–IV**.

Table 4.2: Multivariable-adjusted HRs in the subgroup analysis by alcohol intake of **Paper I–IV***

	Paper I†		Paper II‡	Paper III§	Paper IV¶
Analysis	**Veg**	**Fru**	**GL**	**Total fish**	**Coffee**
Main	**0.83**	1.13	**1.38**	**0.77**	0.97
High alcohol intake‖					
No	0.93	1.10	1.23	0.89	0.96
Yes	**0.60**	1.33	**1.78**	**0.56**	0.97

Fru, fruit; GL, glycemic load; HR, hazard ratio; Veg, vegetables.
*No confidence intervals are presented for consistency with Table 4.1; however, HRs with bold font had *P* values less than 0.05.
†HRs for each 2 additional servings/day.
‡HRs for each 50 additional units/day.
§HRs for 2.4 servings/week compared with 0.9 servings/week (modeled in a non-linear fashion using restricted cubic splines).
¶HRs for each 1 additional cup/day.
‖Defined as an alcohol intake of 12 g or more per day (equal to 1 standard drink of alcohol).

[54] *P* values for interaction were 0.16 (vegetables), 0.56 (fruit), 0.12 (glycemic load), 0.10 (total fish), and 0.77 (coffee); all of which were obtained by adding and testing an interaction term (using the Wald test) between the exposure of interest and the indicator variable for alcohol intake (null hypothesis: the effect of an exposure *does not vary* by levels of alcohol intake [low or high]).

4.2 Recurrence and progression study (Paper V)

4.2.1 Main results

Two hundred fifty-five men and 131 women with non-gallstone-related acute pancreatitis were included in the study, in whom the incident episode had been diagnosed between 1998 and 2013 (median length of hospital stay: 4 days), and who contributed 1859 person-years of follow-up and 90 cases of recurrent and progressive pancreatic disease until the end of 2014. The mean value of the recommended food score (RFS) was 10.3 at baseline, which, simply put, means that an average of 10 recommended food items were consumed on a weekly basis (out of the maximum 25 food items). Baseline and diagnosis characteristics by the RFS are shown in **Table II, Paper V**.

I observed an inverse association between the RFS modeled as a continuous variable and risk of recurrent and progressive pancreatic disease after adjustment for age and sex, albeit only borderline in statistical significance (*P* for overall association = 0.06), but it became weaker and was clearly not statistically significant after adjustment for other potential confounders (including clinical characteristics) (*P* for overall association = 0.27). The HR for each 2-unit increase in the RFS (equal to 0.5 SDs of its distribution and corresponding to a weekly consumption of 2 healthy food items) was 0.92 (95% CI, 0.81–1.06), with no evidence of departure from the assumption of linearity (*P* for non-linearity = 0.78). In the categorical analysis (Figure 4.5), the HR was 0.69 (95% CI, 0.36–1.29) for the highest compared with the lowest tertile of the RFS (*P* for overall association = 0.45).

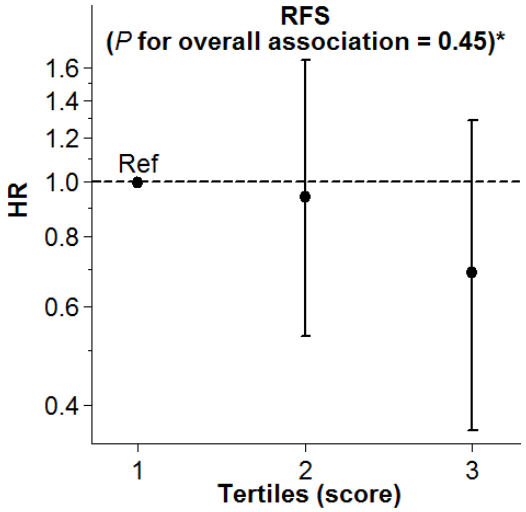

Figure 4.5: Multivariable-adjusted HRs and 95% CIs of recurrent and progressive pancreatic disease by tertiles of the RFS.
*Test for overall association was conducted by testing coefficients of categorical variables jointly equal to zero.

4.2.2 Sensitivity analysis

In the sensitivity analysis that examined changes in diet and other lifestyle factors following a diagnosis of non-gallstone-related acute pancreatitis, for which purpose the RFS was categorized into approximate quartiles, I observed that 83% of the individuals stayed in the same or an adjacent quartile of the RFS

between the questionnaire in 1997 (before the diagnosis) and that in 2009 (after the diagnosis). Using questionnaire data from 2009 to calculate the RFS yielded a similar exposure-outcome association as that in the main analysis (absolute difference in the age- and sex-adjusted HR for each 2-unit increase: −0.04). With respect to cigarette smoking and alcohol drinking, there were on the other hand substantial changes between the 2 questionnaires. Among individuals who had reported that they smoked cigarettes and drank alcohol in 1997—73% and 18%, respectively, reported that they had discontinued these habits by 2009. In addition, among those who reported that they still drank alcohol in 2009, the alcohol intake had decreased by 26 g/week. The results for alcohol use (but not those for the RFS and cigarette smoking) seemed to be directly explained by a diagnosis of non-gallstone-related acute pancreatitis, as was evident by the low discontinuation frequency and the small decrease in alcohol intake when looking the data of everyone who had been eligible for study inclusion (Table 4.3).

Table 4.3: Changes in dietary intake, cigarette smoking, and alcohol drinking between the questionnaire in 1997 and that in 2009*

Analysis	Individuals with non-gallstone-related acute pancreatitis† (*N* = 139)	Participants in the SMC and the COSM‡ (*N* = 46,538)
Changed their food consumption§ (%)	16.9	18.2
Discontinued their use of cigarettes (%)	68.8	62.2
Discontinued their use of alcohol (%)	17.8	7.5
Decrease in their alcohol intake¶ (mean, g/week)	24.0	5.8

COSM, Cohort of Swedish Men; SMC, Swedish Mammography Cohort.
*Mean values in the subset with non-gallstone-related acute pancreatitis were standardized to the sex and age distribution (<77, ≥77 years) of the SMC and the COSM in 2009, whereas percentage values were only standardized to the sex distribution because of zero observations in some of the age-specific strata.
†Consisting of individuals who had been diagnosed with incident disease between 1998 and mid-2009 and who, thereafter, had answered the questionnaire in 2009
‡Consisting of everyone who had been eligible for study inclusion, given that they had answered the questionnaire in 2009.
§Defined as the percentage of participants who did not stay in the same or an adjacent quartile of the recommended food score.
¶Among those who still drank alcohol in 2009.

5 Discussion

In the first section of this chapter, I will discuss the main findings of the association between diet and risk of non-gallstone-related acute pancreatitis, with separate subsections for the incidence studies (**Paper I–IV**) and the recurrence and progression study (**Paper V**) (apart from potential biological mechanisms, which are discussed in the same subsection). That section will be followed by one on methodological considerations of epidemiological research in general and of **Paper I–V** in particular.

5.1 Main findings

5.1.1 Incidence studies (Paper I–IV)

Using data from a large group of middle-aged and elderly Swedish persons (study samples ranging from 71,458 to 81,100 persons), who were enrolled in 2 prospective cohorts (the SMC and the COSM) and followed up for a maximum of 12 to 15 years, I observed that incidence of non-gallstone-related acute pancreatitis (study samples ranging from 320 to 383 cases) had an inverse association with consumption of vegetables (**Paper I**) and total fish (**Paper III**), a positive association with consumption of high-glycemic load foods (**Paper II**), and a null association with consumption of fruit (**Paper I**) and coffee (**Paper IV**). The magnitude of change in the incidence rate was 17% for vegetables (for each 2 servings/day), 23% for total fish (for 2.4 vs. 0.9 servings/week), and 38% for glycemic load (for each 50 units/day; corresponding to around 3 servings of white bread [Foster-Powell et al., 2002]). The findings were similar in men and in women, not to mention that they were consistent across a number of sensitivity analyses (which aimed to account for various sources of underlying biases, such as confounding bias and information bias; both of which will be discussed and explained in the next section). Overall, these findings suggest that diet, a previously overlooked factor, might be important in the primary prevention of non-gallstone-related acute pancreatitis.

Because epidemiological studies have shown that only a minority of alcohol drinkers develop acute pancreatitis, even those who drink more than 60 to 80 g/day (Kristiansen et al., 2008; Lankisch, Lowenfels, & Maisonneuve, 2002),[55] it has long been suggested that the pancreas' susceptibility to alcohol-related acute pancreatitis must be modified by genetic and environmental factors (Apte, Pirola, & Wilson, 2008; Lankisch et al., 2015; Pandol et al., 2011).[56] Diet is often mentioned as one of the potential modifiers of the alcohol-acute pancreatitis association—and thus, I examined whether the exposure-outcome associations in **Paper I–IV** varied by levels of alcohol intake. Interestingly, the association with vegetable consumption, high-glycemic load diets, and total fish consumption seemed to be stronger in persons who drank 1 or more standard drinks of alcohol per day than in those who drank less (1 drink equal to 12 g of pure alcohol). Although these findings should be interpreted with care due to the low

[55]Remember that alcohol abuse (alongside gallstones) is considered to be the most important risk factor for acute pancreatitis.
[56]In other words: there might be a biological interaction between alcohol intake and other covariates (modifiers or interaction variables).

number of cases in each strata, which lead to a large imprecision in the estimates, they are suggesting that diet might have a role in the pancreas' susceptibility to alcohol.

5.1.1.1 Comparison with other studies

As detailed in the Background chapter (section 1.4), the epidemiological literature on the association between diet and risk of acute pancreatitis is sparse. Also, it has seldom been made clear what type (incident, recurrent, or acute-on-chronic) and subtype (gallstone-related or non-gallstone-related) of acute pancreatitis that has been studied. I will go through the available literature in detail below, with the exception of ecological studies (because the evidence from such studies is considered weak) and studies that did not study the same (or even similar) dietary factors as did **Paper I–IV** (because the between-study comparability is very limited). (Details on ecological studies, as well as on 3 other observational study designs, are outlined in Table 5.1.)

Prior to the publication of **Paper I–IV,** 2 case-control studies had been published on the association between carbohydrate intake[57] and risk of acute pancreatitis. Sarles et al. (1965) observed that French men and women with acute pancreatitis (n = 22) tended to have a lower carbohydrate intake than disease-free controls; whereas Wilson et al. (1985), who used persons with alcohol-related cirrhosis as their control group (in order to "[overcome the difficulty that] involves the study of two variables—alcohol intake and the presence or absence of pancreatitis" [Wilson & Pirola, 1986]), found a tendency towards a higher carbohydrate intake in Australian men and women with alcohol-related acute pancreatitis (n = 20). In 2 later case-control studies, Segal et al. (2000) observed that a weekly consumption of fruit (but not vegetables) had an inverse association with risk of acute pancreatitis in black South African men and women (n = 30 cases), while Mitta et al. (2011) found a positive association with consumption of fresh water fish (as opposed to salt water fish) and risk of acute pancreatitis in Indian men (n = 75 cases).[58] Overall, the comparisons with **Paper I–IV** are halting because of several reasons, including (but not limited to) differences in study design (ie, cohort vs. case-control), outcome definition (eg, non-gallstone-related vs. mixture of gallstone-related and non-gallstone-related), diet assessment (eg, non-quantitative vs. quantitative), and ethnic distribution (eg, non-Hispanic whites vs. blacks or Asians). It might also be worth to mention that the study by Mitta et al. (2011) only reported crude (unadjusted) estimates and that the authors later speculated that "[p]arasitic infestation of fresh water fish… may be one such reason" why a positive association was observed in their study population (Barreto, 2015). Lastly, using data from a large, prospective cohort study of 128,934 US men and women, who were recruited in 1978 to 1985 and followed up through 1998, Morton et al. (2004) observed that coffee consumption was inversely associated with risk of alcohol-related acute pancreatitis (n = 82); the multivariable-adjusted HR was 0.5

[57] To my knowledge, there is no other study than **Paper II** that has examined the role of glycemic load and glycemic index; therefore, I will compare its results with those from studies on carbohydrate intake.

[58] There is also a Chinese case-control study (ncbi.nlm.nih.gov/pubmed/15208996) in which, amongst others, it is reported that "[oftentimes] eating… green vegetable…were inversely associated with [acute pancreatitis]". However, as only the abstract was available in English, I did not mention it in **Paper I** or in the Background chapter of this thesis.

(95% CI, 0.2–0.99) for 4 or more cups/day compared with 0 cups/day. No association was seen for the episodes of non-gallstone-related pancreatitis that were classified as idiopathic (unknown cause). The potential reasons for the discrepancy in results have been detailed in **Paper IV** but could, in brief, be due to differences in exposure distribution (consumption of <1 cup/day: 5% vs. 41%), incidence rates of non-gallstone-related acute pancreatitis (37 vs. 15 cases per 100,000 person-years),[59] or ethnic distribution (non-Hispanic whites vs. ethnically heterogeneous; with indications that the inverse association was stronger in blacks [HR, 0.5; 95% CI 0.2–1.3] than in whites [including Hispanic whites] [HR, 0.9; 95% CI 0.3–2.5]).

Following the publication of **Paper I–IV**, 2 large prospective cohort studies on the association between several food items and nutrients (including fruit and vegetables, coffee, and carbohydrates) and risk of acute pancreatitis have been published, one as an original article (Prizment et al., 2015) and the other as a conference abstract (Setiawan et al., 2015). Using data on 36,436 women in the Iowa Women's Health Study, who had completed a baseline questionnaire in 1986 (then aged 55 to 69 years) and were followed up for pancreatitis (either acute or chronic) from the date they turned 65 years until the end of 2004 via linkage to the Centers for Medicare Services, Prizment et al. observed neither a statistically significant association between fruit and vegetable consumption (*P* for overall association = 0.50) nor between carbohydrate intake (*P* for overall association = 0.47) and risk of acute pancreatitis (*n* = 460 cases). The multivariable-adjusted odds ratio was 0.89 (95% CI, 0.67–1.18) for fruit and vegetable consumption (comparing ≥31.5 servings/week with ≤15.5 servings/week) and 1.15 (95% CI, 0.79–1.66) for carbohydrate intake (comparing ≥260 g/day with ≤160 g/day). Although there are several explanations to why the magnitude and statistical significance of these results are different from those in **Paper I** and **II** (eg, non-separation of fruit and vegetables as well as differences in exposure and age distribution), the most important one is that the cohort only consisted of elderly women, meaning that the proportion of gallstone-related acute pancreatitis should have been very high. (In fact, many of the exposure-outcome associations that Prizment et al. present in their Table 2 are highly similar to those on symptomatic gallstone disease that I present in Table S.1 [which, in turn, are in contrast to those on non-gallstone-related acute pancreatitis], such as a null association with cigarette smoking, an inverse association with alcohol intake, and a null association with vegetable consumption.) My initial enthusiasm for this study was rather high; however, upon a more detailed reading,[60] a number of methodological issues became apparent. First, as indicated by the use of an odds ratio to measure the exposure-outcome association, the authors did not account for differences in time-at-risk, which, inevitably, must have led to a bias (assuming that the time-at-risk *was the same for all participants* is not correct; especially if we consider that the participants were followed up from age 65 years and onwards [an age they achieved sometime between 1986 and 1996], with the maximum follow-up period ranging from 9 to 19 years). I initially

[59]Despite the fact that the estimate from Morton et al.'s study is based on the combination of acute and chronic pancreatitis (individual data on acute pancreatitis was only given for alcohol-related episodes).
[60]I was actually asked to be a reviewer of this manuscript but had, for reasons of vacation and parental leave, to decline that opportunity.

thought that the authors had performed a nested case-control study,[61] but I found no indication of such when I read the study. Second, the authors could not account for previous history of acute or chronic pancreatitis, neither at baseline nor at the start of follow-up, which left the possibility that (*i*) cases were not incident and (*ii*) exposures and covariates had changed due to a diagnosis of acute or chronic pancreatitis.[62] Finally, the authors categorized cases as "[acute pancreatitis], if women had one [acute pancreatitis] episode and [as] [chronic pancreatitis], if women had two or more episodes of [acute pancreatitis] that were at least 6 weeks apart or one episode of [chronic pancreatitis]". As a result, women with 2 separate episodes of acute pancreatitis, even if the episodes had occurred 19 years apart, were not considered to have had acute pancreatitis but rather to have had chronic pancreatitis, which, at least in my opinion, is highly questionable. The final study that I would like to mention is the one presented by Setiawan et al. (2015) as a conference abstract at the 46th Meeting of the American Pancreatic Association in November, 2015. Using data from a large, prospective cohort study of 145,886 middle-aged and elderly US men and women, who were enrolled in the Multiethnic Cohort (for details of the cohort, please see Kolonel et al. [2000]) and followed up via hospitalization claim files between 1993 and 2012, the authors observed that "[d]ietary intakes of saturated fat and cholesterol, and their food sources (eg, red meat, eggs, and shellfish), were positively associated with pancreatitis, whereas intakes of fiber, vitamin D, and coffee were inversely associated with variation by pancreatitis types". (n = 2810 cases, of which 1222 were categorized as non-gallstone-related acute pancreatitis.) Although that statement does not contain sufficient information for any sort of comparison with **Paper I–IV**, it is likely that most of the exposures that I have examined are included in their analysis. As such, and especially given its very large size, I am looking forward to read that study in detail when, and if, it is published as an original article.

5.1.2 Recurrence and progression study (Paper V)

Using data on a total of 386 persons with non-gallstone-related acute pancreatitis in the SMC and the COSM, in whom the incident diagnosis had been given between 1998 and 2013, and who were subsequently followed up until the end of 2014 (mean follow-up of 4.8 years), I observed no clear association between overall diet quality (using a recommended food score [RFS]) and risk of recurrent and progressive pancreatic disease (study sample of 90 cases). While a weak (in terms of statistical significance) inverse association was observed in the age- and sex-adjusted analysis, it lost all of its statistical significance in the multivariable-adjusted analysis (although its magnitude was only slightly attenuated). The magnitude of change in the recurrence and progression rate was 8% for each 2 units increase in the RFS, which corresponds to a weekly consumption of 2 extra healthy food items (eg, 1 serving of tomatoes and 1 serving of fatty fish).

---

[61] A nested case-control study is a case-control study within a cohort study, meaning that both cases and controls are recruited from the same study population. If Prizment et al. had used a frequency-based density sampling, the controls would have been sampled to represent the distribution of person-time in the study population with respect to exposure.

[62] This could lead to reversed causality, the situation of an outcome preceding and causing an exposure instead of an exposure causing an outcome.

Many leading experts on acute pancreatitis argue that alcohol counseling should always be part of its secondary prevention, irrespective of the episode being classified as alcohol-related or not (Johnson et al., 2014); as was previously mentioned in the Background chapter (subsection 1.2.2.3). That recommendation is supported, at least for patients with a very high alcohol intake, by a randomized clinical trial from Finland in which the 2-year risk of recurrent alcohol-related acute pancreatitis was lower in patients who received an aggressive alcohol counseling (at discharge and at every 6 months thereafter) than in those who received it at discharge only (Nordback et al., 2009). (The mean alcohol intake was 48 to 56 g/day in the 2 arms of that trail, with 39 to 44% of them having a prior conviction of drunken driving.) It is unclear, however, how good (or bad) the patient compliance is to the type of alcohol counseling that is performed in a more "everyday setting", especially if the patients' alcohol intake is low to begin with (as it was in **Paper V**, with a mean intake of 16 g/day). A highly interesting finding of **Paper V** was, therefore, that almost one-fifth of the study population had stopped drinking alcohol between 1997 and 2009; that is, before and after their incident episode of non-gallstone-related acute pancreatitis. The individuals who had continued to drink alcohol also did so with greater moderation after their diagnosis (mean difference: −26 g/week). Thus, encouragingly enough, it does seem as if patients with acute pancreatitis listen to their physicians' advice on alcohol use, even when their alcohol intake is rather low.

5.1.2.1 Comparison with other studies

To the best of my knowledge, **Paper V** is the first study to examine the association between diet and risk of recurrent and progressive pancreatic disease among individuals who have had acute pancreatitis. However, there are several studies on the discontinuation frequency of alcohol use. In addition to the randomized clinical trial that was discussed above (Nordback et al., 2009), in which 16% of the study population reported that they had abstained from alcohol throughout the trial, the same research group found a similar percentage of alcohol abstainers (19%) in another study population of alcohol-related acute pancreatitis (mean alcohol intake of 67 g/day) (Pelli, Lappalainen-Lehto, Piironen, Sand, & Nordback, 2008). Furthermore, even higher discontinuation frequencies have been reported in German (45%) (Lankisch et al., 2009) and Dutch studies (49%) (Ahmed Ali et al., 2016), with alcohol-related acute pancreatitis defined as a self-reported alcohol intake of more than 40 to 60 g/day. Thus, the discontinuation frequency that I observed in **Paper V** is not unique in itself (even though it has never been reported for patients with a fairly low alcohol intake), but the setting in which it was observed is clearly unique—a large, prospective cohort study that was representative of the general population. In contrast, the other studies had recruited their participants in a hospital setting, with the specific purpose to study acute pancreatitis. As such, the physicians may have been extra motivated in their alcohol counseling (due to the planned research project) and the participants should have been highly motivated to participate in the study and to decrease their alcohol intake, which, in combination, might limit the generalizability of the results. Furthermore, the level of social desirability bias (ie, bias due to the desire of giving socially accepted answers) is expected to be extremely high with respect to alcohol intake in a

pancreatitis-specific study. For these reasons, I believe that **Paper V** provides the most unbiased results to date on the effect of physicians' alcohol counseling on the discontinuation of alcohol use.

5.1.3 Potential biological mechanisms

Potential biological mechanisms that might explain the association between diet and risk of non-gallstone-related acute pancreatitis are mostly speculative, which goes hand-in-hand with the lack of epidemiological data on the association. Researchers have long speculated that *if* diet has a role in the development of acute pancreatitis, it ought to be due to high-fat and high-protein meals and their potential to stimulate intestinal release of CCK and lead to subsequent secretion of digestive enzymes (Thomas, Mah, & Barreto, 2012). As detailed in the Background chapter (subsection 1.2.1), the infusion of supramaximal concentrations of CCK is the most common way to induce acute pancreatitis in experimental settings (Saluja et al., 2007)—although less than one-tenth of the required concentrations are likely to be reached in humans (Gorelick & Thrower, 2009). In addition, of the dietary factors that were studied in **Paper I–IV**, it is only consumption of total fish (due to its rich content of protein and fat) (Keller & Layer, 2005) and coffee (Douglas, Jansen, Tham, & Lamers, 1990) that should have stimulated the intestinal release of CCK to a significant extent, indicating that there must be other biological mechanisms that are involved in the association between diet and risk of non-gallstone-related acute pancreatitis (especially if one is to consider that the association with total fish consumption in **Paper III** was inverse in its direction). (Nonetheless, I have contemplated whether stimulation of CCK might be a partial explanation to the non-linear association in **Paper III**, with an apparent plateau at 2.0–3.0 servings/week. This seems a somewhat unlikely explanation, though, given that many other studies have observed non-linear associations between fish consumption or LCn-3 PUFAs and risk of various, non-CCK-related outcomes, such as atrial fibrillation [Rix et al., 2014], rheumatoid arthritis [Di Giuseppe et al., 2014], and preterm birth [Klebanoff et al., 2011].)

A potential biological mechanism that has been heavily featured in **Paper I–V**, and which I personally believe is of major importance, is the indirect effect of diet on the incidence of diabetes, obesity, and hypertriglyceridemia—that is, potential risk factors for acute pancreatitis (as summarized in Table 1.1). Also, given that increased concentrations of reactive oxygen species and inflammatory cytokines[63] have been implicated in the pathophysiology of acute pancreatitis (Leung & Chan, 2009; Sah & Saluja, 2011), an association between diet and risk of non-gallstone-related acute pancreatitis is biologically plausible because of the antioxidant and anti-inflammatory properties of food items (or as in the case of high-glycemic load diets, because of its pro-oxidant and pro-inflammatory properties). Figure 5.1 gives a schematic overview of these mechanisms in the context of **Paper I–IV**. (For additional details, as well as information on other potential mechanisms, such as dietary effects on calcium and adiponectin concentrations, I refer the reader to the Discussion section of each individual study.)

[63] According to its MeSH-term, a cytokine is defined as a "non-antibody protein secreted by inflammatory leukocytes and some non-leukocytic cells, that act as intercellular mediators [of cell signaling]" (ncbi.nlm.nih.gov/mesh/68016207).

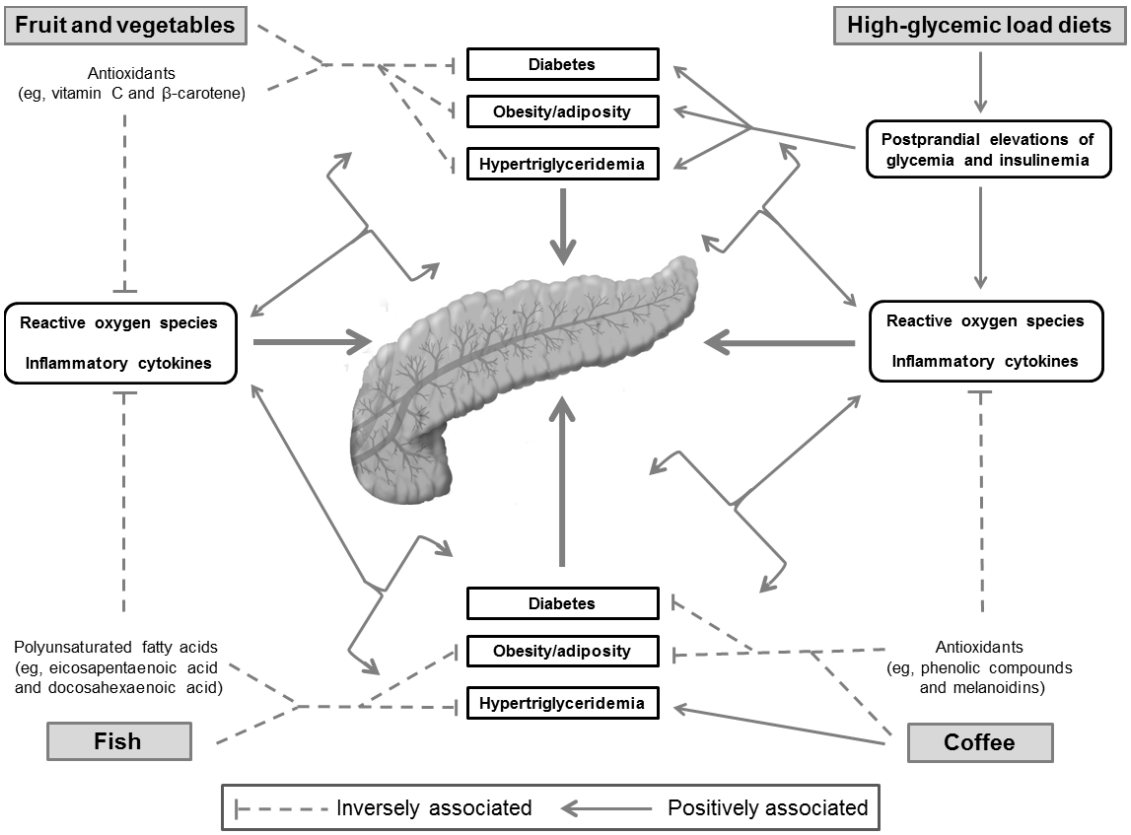

Figure 5.1: Schematic overview of some of the (potential) biological mechanisms that might explain the association between diet and risk of non-gallstone-related acute pancreatitis. For references, please see subsection 1.2.1, section 1.3, Table 1.1, and Table 3.3. Modified from Wikimedia Commons (commons.wikimedia.org/wiki/File:Duodenumandpancreas.jpg) (CC0).

In hindsight, I probably put too much emphasis on the role of dietary antioxidants in the Discussion section of **Paper I**, while, at the same time, I oversimplified the complexity of the pathophysiology of acute pancreatitis; especially when I used phrases as "[s]ince both vegetables and fruit are rich in antioxidants, the lack of inverse association between fruit and risk of non-gallstone-related acute pancreatitis was unexpected." Although fruit and vegetables have similar contents of bioactive compounds, they are far from identical and have well-known differences in the type and amount of dietary antioxidants, dietary sugars, and dietary fibers. As a consequence, one or several of these differences could explain why I observed an inverse association with vegetable consumption but not with fruit consumption (not to mention that it could be explained by some sort of bias, which will be discussed in the next section). It should also be noted that in other studies that have separated vegetable consumption from fruit consumption, there have been differences in their associations with risk of some diseases, such as cognitive decline and cancers (Appleton et al., 2016). Regardless, it is too simplistic to reduce the association between a dietary factor and risk of non-gallstone-related acute pancreatitis (or any other disease) to nothing more than its content of antioxidants. If that had been the case, a very strong exposure-outcome association should have been seen for coffee consumption, because it is one of the major contributors to the antioxidant capacity[64] of the diet (Natella & Scaccini, 2012). Likewise, with

[64]Antioxidant capacity can be defined as a "concept aiming to measure the total antioxidant defense system in reducing reactive species by taking synergistic and antagonistic interactions between compounds into account" (Rautiainen Lagerström, 2012).

regard to the association between total fish consumption and risk of non-gallstone-related acute pancreatitis in **Paper III**, I observed that the exposure-outcome association with fatty fish consumption was similar to that with lean fish consumption; indicating that any underlying mechanism is more complex than being solely due to the content of LCn-3 PUFAs.

The above discussed biological mechanisms might also lead to a lower (or higher) risk of recurrent and progressive pancreatic disease. However, with respect to the statistical validity of the Cox regression model, I did not consider it possible to examine individual food items in **Paper V**. The number of events per parameter was low to begin with, which may have led to biases in HRs and 95% CIs (Vittinghoff & McCulloch, 2007), and inclusion of multiple food items would have made that number even lower. One advantage of studying a dietary pattern is that it accounts for the whole diet, including interactions between food items with different nutrient contents. This is especially true compared with individual food items or nutrients, which only reflect a small piece, or a snapshot, so to speak, of the whole diet. However, as was evident in **Paper I–IV**, it is possible that only certain food items are capable of influencing the risk of non-gallstone-related acute pancreatitis, irrespective of the disease being incident, recurrent, or progressive. Therefore, the RFS and other indicators of overall diet quality might be of little value when the aim is to study the role of diet in the development, recurrence, and progression of non-gallstone-related acute pancreatitis.[65]

[65]In a secondary analysis of this thesis, I created a RFS that did not contain any fruit items (n = 4), which, interestingly enough, had a seemingly stronger association with risk of recurrent and progressive pancreatic disease than had the original RFS. The multivariable-adjusted HR for each 2-unit increase in the modified RFS was 0.87 (95% CI, 0.74–1.02).

5.2 Methodological considerations

5.2.1 Study design

This thesis is solely comprised of prospective cohort studies, which, in general, is the type of observational study design that provides the highest level of evidence (Table 5.1).[66] If properly conducted, the prospective cohort design reduces the likelihood of reversed causality (compared with cross-sectional studies, in which the outcome might precede the exposure) and recall bias (compared with case-control studies, in which the cases might recall the exposure differently than the controls) (Rothman, Greenland, & Lash, 2008). It is important to stress, though, that all observational study designs have in common that they reflect *associations with diseases* rather than *causes of diseases*.

Table 5.1: Examples of different types of observational study designs in epidemiological research*

Study design	Level of evidence†	Characteristic	Example
Ecological study	(1/4)	A study in which the exposure and outcome is measured on the population level	We collect multi-county data on the average FV consumption and the incidence of AP, whereafter we compare if the counties with a high consumption have a lower incidence of AP than those with a low consumption
Cross-sectional study‡	(2/4)	A study in which the exposure and outcome is measured at the same point in time	We send a survey to 1000 people and ask (*i*) how much FV do you eat and (*ii*) have you had a diagnosis of AP, whereafter we compare if the persons with a high consumption have a lower prevalence of AP than those with a low consumption
Case-control study§	(3/4)	A study in which the exposure is measured retrospectively in persons with and without an outcome	We collect data on FV consumption from 100 persons who have had AP and 400 disease-free persons (controls), whereafter we compare if the odds of being a case of AP were lower for the persons with a high consumption than those with a low consumption
Prospective cohort study	(4/4)	A study in which exposed and non-exposed persons (who have not had an outcome) is followed up prospectively until they experience the outcome	**Paper I** of this thesis

AP, acute pancreatitis; FV, fruit and vegetables.
*Other study designs are case studies, case series, and proportional mortality studies.
†(4/4) equals the strongest evidence.
‡In cross-sectional studies, only the prevalence (or prevalence rate) of a disease can be studied (ie, the total number of cases of a given disease [new and pre-existing] in a specified population at a particular time).
§Even though the exposure assessment in case-control studies is most often retrospective, it can also be prospective (ie, before the onset of a disease). One such example is when a case-control study is nested within a prospective cohort study.

A potential limitation of the study design in **Paper V** was that the individuals had to have "completed" a 90-day post-diagnosis window (Figure 5.2, left), during which (*i*) diagnoses of chronic pancreatic diseases and gallstone-related acute pancreatitis were not allowed and (*ii*) acute pancreatitis-related hospital care was considered to be part of the initial episode. Although chosen as an inclusion criterion for a reason (ie, as previously mentioned [subsections 3.4.2 and 3.5.2], to obtain a study population that

[66]Epidemiological studies can also be experimental (eg, randomized clinical trials), which means that the researcher is controlling (instead of observing) the primary exposure (eg, administration of a specific drug).

consisted only of persons with incident non-gallstone-related acute pancreatitis as well as to limit the influence of early readmissions of acute pancreatitis), the consequence was that I did not account for incident episodes that led to death or recurrent episodes that happened very early. The potential implications of this delayed entry (so-called left truncation) with respect to pancreatitis-related death are illustrated via the directed acyclic graph (DAG)[67] in Figure 5.2 (right). Following the example by Bonn (2015), I will let X represent an indicator of the exposure (ie, overall diet quality), I an indicator of inclusion into the study (ie, survival up to the truncation point), D an indicator of recurrent or progressive pancreatic disease during the follow-up period, and U an indicator of all potential confounders, irrespective of them being measured or not. To further simplify the discussion, I will assume that each indicator is binary (0/1) and that 1 equals exposed (X and U), survival (I), or case (D). Because of the left truncation, I am forced to study the association between X and D conditional on I being equal to 1 (ie, survival up to the truncation point). As such, a spurious association (pathway) between X and D via U is being opened through I. However, it can be argued that its direction is opposite to that of the direct association (pathway) between X and D, thereby leading to conservative HRs in the Cox regression model. To exemplify this, let us look at the individuals who (*i*) survived up to the truncation point ($I = 1$) and (*ii*) had a low overall diet quality ($X = 0$). In general, it is reasonable to expect that a low diet quality and a low nutritional status is going to be associated with an increased probability of pancreatitis-related death during the first 90 days of the diagnosis ($I = 0$). So, to "explain" why these individuals did not die, it must be that their probability of being unexposed to important confounders were increased ($U = 0$). In turn, and despite their unhealthy eating, the probability that recurrent or progressive pancreatic disease developed during the follow-up period should have been decreased ($D = 0$).

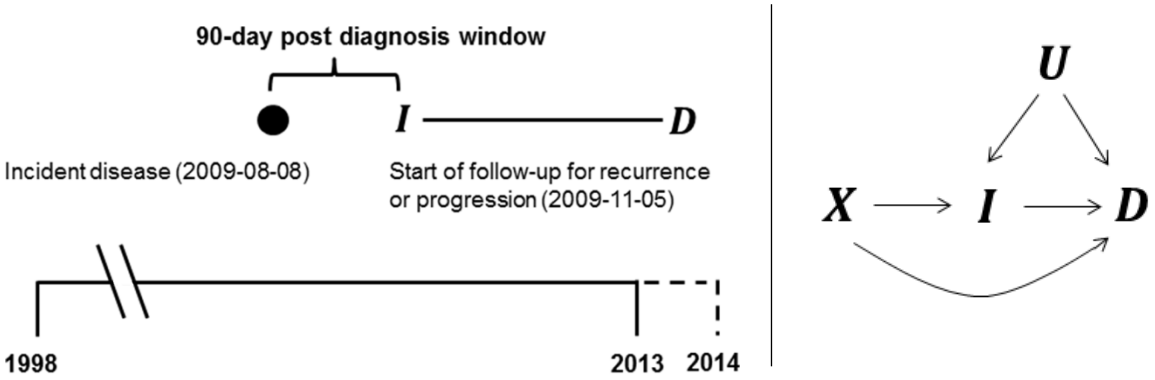

Figure 5.2: Example (left) of a patient who (*i*) was diagnosed with incident non-gallstone-related acute pancreatitis during the recruitment period (1998 to 2013), (*ii*) "completed" the 90-day post-diagnosis window, and (*iii*) entered the follow-up (denoted "I") for recurrent and progressive pancreatic disease until 2014 (denoted "D"); and example (right) of a DAG[67] on the implications of delayed entry (so-called left truncation) into the study (X = exposure; I = study inclusion [survival]; D = case status; and U = confounder).

[67]DAGs are tools to visualize the pathways by which an exposure might lead to an outcome (seen in the framework of causation) (Greenland, Pearl, & Robins, 1999) The idea is to determine the variables on which it is necessary to condition on in order to control for confounding of causal effects. The term *acyclic* means that the graph contains no feedback loops; that is, if X causes Y, Y cannot cause X at the same moment.

5.2.2 Random error

Random error refers to the random (chance) deviation of individual measurements from the average of a population of measurements, which always occurs when study subjects are sampled. A high degree of random error is associated with a low precision of the risk estimation, and vice versa. In general, the precision of an epidemiological study is indicated by 95% CIs and is foremost dependent on the sample size (and especially on the number of cases) (Rothman et. al, 2008). Formally, as detailed in subsection 3.6.2, an exposure-outcome association is considered to be statistically significant if the 95% CI does not include 1 (P value < 0.05), whereby the null hypothesis can be rejected ("exposure X *has no effect* on outcome Y").[68] With respect to hypothesis testing, there are 2 types of errors that might occur: (*i*) the null hypothesis is rejected when it is true (a so-called type I error) and (*ii*) the null hypothesis is not rejected when it is false (a so-called type II error). A related measure is the statistical power, which is the probability to correctly reject a null hypothesis (1-the probability of a type II error).

The number of cases in **Paper I–IV** (n = 320 to 383) and **Paper V** (n = 90) was fairly limited, which lead to a moderate precision of the HRs.[69] The statistical power was as a consequence also limited, meaning that the exposure-outcome associations had to be strong (in terms of magnitude) for the null hypotheses to be correctly rejected; as is exemplified in Table 5.2 with respect to positive (vegetable consumption and glycemic load) and null findings (coffee consumption and the RFS). While there was enough statistical power to reject the null hypothesis for HRs on the order of what I observed in **Paper I** and **II**, it was not so for HRs on the order of what I observed in **Paper IV** and **V**. Thus, the possibility of a type II error cannot be fully excluded as an explanation to the null findings in **Paper IV** and **V**. Likewise, the possibility of a type I error cannot be fully excluded as an explanation to the positive findings in **Paper I–III**—as it never can when multiple (or even a single) associations are being tested (Boffetta et al., 2008).[70]

Table 5.2: Comparison between the HRs that were observed in **Paper I**, **II**, **IV**, and **V** and those that were needed to be observed in order to obtain a statistical power of 80%*

	Paper I	Paper II	Paper IV	Paper V
	Veg	GL	Coffee	RFS
Magnitude of HRs†				
Needed to be observed (for statistical power of 80%)‡	0.63	1.53	0.58	0.50
De facto observed (multivariable-adjusted estimates)	0.56	1.60	0.84	0.69

GL, glycemic load; HR, hazard ratio; RFS, recommended food score; Veg, vegetables.
*Although arbitrary (Cohen, 1988), 80% is considered to be an appropriate level of statistical power.
†HRs for the highest compared with the lowest category of consumption and/or score of each exposure.
‡Calculated using the Episheet software developed by Rothman (2002) (with 2-tailed α = 0.05).

[68] Although already mentioned in the Results chapter (footnote 52), I would like to once again stress that 95% CIs and P values say nothing about whether an association is true or spurious. To make such a statement, the association has to be viewed in the context of previous evidence, biological plausibility, and systematic errors.
[69] As an example, in **Paper IV**, the 95% CIs ranged between 0.59 and 1.20 (HR, 0.84) for the highest compared with the lowest category of coffee consumption. When Discacciati et al. (2013) used localized prostate cancer as the outcome in the COSM (n = 2368), the 95% CIs ranged between 0.69 and 0.96 (HR, 0.81) for the same comparison.
[70] This is of particular concern in genome-wide association studies, in which up to 1 million genetic variants may be tested for their individual association with a certain disease (Rice, Schork, & Rao, 2008).

5.2.3 Systematic error (bias)

Systematic error, also called bias, refers to the systematic (fixed) deviation of observed values from the true values of a measurement of interest. In contrast to random error, it is not reduced by increasing the sample size of a study (Rothman et al., 2008). Systematic errors might skew the risk estimates towards the null (ie, HRs closer to 1), away from the null (ie, HRs further from 1), or even across the null (eg, HRs > 1 become < 1). In the forthcoming subsections, I will discuss the 3 major categories of systematic errors: selection bias, information bias, and confounding bias. (For a brief overview of systematic errors, including their type and the study designs in which they can occur, please see Delgado-Rodríguez & Llorca [2004]. In total, more than 70 systematic errors are listed by the authors.)

5.2.3.1 Selection bias

According to Rothman et al. (2008),[71] selection bias is defined as "distortions that result from procedures used to select subjects and from factors that influence study participation". It arises when, and if, inclusion or follow-up of participants is related to *both* the exposure and the outcome, whereby the exposure-outcome association might be different according to participation status. A selection bias can be introduced during the recruitment of participants (common in case-control studies) or during the tracing of participants to ascertain their outcome status (common in cohort studies).[72]

While, in general, the role of selection bias is thought to be limited during the recruitment phase in a prospective cohort setting (because study participation, no matter how high or low it might be, cannot be conditional on an outcome that has yet to occur),[73] the delayed entry (left-truncation) that was used in **Paper V** is likely to have introduced some degree of selection bias (so-called survival bias) (see subsection 5.2.1 for details). (I would like to point out that I use the same definition of selection bias as do Rothman et al. [2008], which, for example, means that non-response bias and missing information bias resulting from differential selection at recruitment are viewed as confounding bias, because none of them can be conditional on an outcome that has not yet occurred.) Because data were linked to various national health registers, each of which had an almost complete national coverage during the study period (see subsection 3.1.2 for details), the role of selection bias during the follow-up phase of **Paper I–V** was also likely to be limited, with one notable exception: I did not account for migration out of Sweden. It has been reported that Swedish emigrants are more likely to be well-educated (Westling, 2012). A high education was, in turn, associated with a healthier eating in **Paper I–V** (as shown in **Table I** or **II** of each individual study). Therefore, if we use **Paper I** as an example, it is possible that those who had the highest

[71] Kenneth J. Rothman (b. 19XX) is a leading researcher and expert in epidemiology. He has authored 2 textbooks on epidemiological methods (2008, 2012); both of which are heavily cited in this thesis. A brief interview with him from 1998 is available via sciencedirect.com/science/article/pii/S0140673605611130

[72] In the latter scenario, the exposure and the outcome is related to the success of the prospective tracing (so-called completeness of follow-up) and not to the study participation at recruitment.

[73] Although one could argue that there is a certain level of "built-in selection bias" of old people during the recruitment phase of cohort studies, simply because their participation is conditional on being alive and outcome-free at the study start (and thus, less susceptible to the outcome). This is exemplified by Hernán, Alonso, & Logroscino (2008), who discuss the role of selection bias in the age-specific association between smoking and risk of dementia.

consumption of vegetables were most likely to have moved out of Sweden during the follow-up period—while, at the same time, their outcome status could not be assessed. As a result, the HR for the highest compared with the lowest quintile of vegetables consumption might have been biased away from the null.[74] To estimate the magnitude of such a selection bias, or at least try to do so, I used data from Statistiska centralbyråns statistikdatabas (2016a; 2016b) on the percentage of men and women (aged 45 to 84 years) who had emigrated from Västmanland County in 1998 (0.1%). By assuming that this percentage applied to Uppsala and Örebro counties too, and that it had been constant during the follow-up period, 1375 persons from the SMC and the COSM were estimated to have left Sweden at some point, in whom a total of 5 cases of non-gallstone-related acute pancreatitis were expected to have occurred (assuming that their risk was the same as the overall risk in **Paper I** [320/80,019]). However, the HR for the comparison of extreme quintiles was unaltered in a sensitivity analysis in which I assumed that all 5 cases were to have happened in the highest quintile of vegetable consumption (the unadjusted HR [95% CI] changed from 0.45 [0.31–0.64] to 0.50 [0.35–0.71]). Using an even more stringent assumption, say, that the emigration had increased by 0.05% per year since 1998 (which, by all means, is incorrect; especially in a closed cohort setting in which no-one can enter the study after baseline), did neither change the results (HR, 0.63; 95% CI, 0.46–0.88). Thus, even though my future studies should use date of migration as a censoring event (using data from Statistiska centralbyrån), it seems as if selection bias due to differential loss to follow-up is unlikely to have substantially affected the results of **Paper I–V**.

5.2.3.2 Information bias

Information bias refers to the systematic errors that occur at the time of data collection, either in the ascertainment of participants' measurements (ie, exposures and covariates) or in the ascertainment of their outcome status. The most common information bias is called misclassification bias (or measurement error bias), which is further divided into that which is *differential* (dependent on the values of other variables) and that which is *non-differential* (not dependent on the values of other variables).

Misclassification of exposure

Diet was assessed by self-reported FFQs in **Paper I–V**, which, inevitably, is associated with some degree of misclassification because of within-person variation and/or incorrect recall and reporting (Willett, 2013).[75] However, any misclassification is expected to be non-differential between cases and non-cases in a prospective cohort setting (or more simply put, the exposure misclassification cannot be related to the future occurrence of an outcome). In addition, since **Paper I–V** almost exclusively used the questionnaire data from 1997, there was only one round of diet assessment available (at baseline), leaving the possibility of further non-differential misclassification during the follow-up period (**Paper I–V**) as well as after an incident episode of non-gallstone-related acute pancreatitis (**Paper V**). However, the overall diet quality

[74]However, if selection bias had been the only explanation to the results of **Paper I**, I would have expected the exposure-outcome association with fruit consumption to be identical to that with vegetable consumption.
[75]As shown in section 3.2, the correlation between the FFQ-based estimates and those from repeated diet records ranged from 0.4 (vegetable items and lean fish items) to 0.8 (total glycemic load score).

was fairly stable over time (as shown in Table 4.3, with around 80% of the participants staying in the same or an adjacent quartile of the RFS between 1997 and 2009, irrespective if they had had a diagnosis of non-gallstone-related acute pancreatitis or not)—as was the consumption of, amongst others, fruit and vegetables (stability: 77 to 79%), glycemic load diets (stability: 78%), and total fish (stability: 84%).[76] It should be noted that it is difficult to predict how a non-differential exposure misclassification might have biased the results of **Paper I–V**. In contrast to popular misconceptions ("non-differential misclassification of an exposure biases effect estimates toward the null"), non-differential exposure misclassification can sometimes produce a bias away from the null if, for example, the exposure variable has more than 2 levels (Rothman et al., 2008; Vanderweele & Ogburn, 2012).

While exposure misclassification is expected to be non-differential with respect to the future occurrence of an outcome, it might very well be differential with respect to other factors that are measured at baseline. A notable example in the setting of nutritional epidemiology is that obese people are known to underreport their diet to a larger extent than do non-obese people.[77] In a study by Mendez et al. (2011), it was observed that underreporters of energy intake (who were 3 to 4 times more likely to be obese than to be of normal weight) reported higher consumption of healthy food items, such as vegetables and fruit. Thus, if we once again use **Paper I** as an example, it is possible that obese participants tended to overreport their vegetables consumption at the same time as they had an increased risk of non-gallstone-related acute pancreatitis (Sadr-Azodi, Orsini, et al., 2013). As a consequence, the HR for the highest compared with the lowest quintile of vegetables consumption might have been biased towards the null. (Likewise, this could be a partial explanation to why the HR for the highest compared with the lowest quintile of fruit consumption, albeit not statistically significant, was > 1.) Although I tried to account for misreporting of diet by excluding participants who had reported an implausible energy intake at baseline (see section 3.5 for definition and details), it has been shown that this method has a questionable effect (Mendez et al., 2011). Therefore, in my future studies, I should try to use another method; for example, the Goldberg method or the predicted total energy expenditure method. Furthermore, although not a misclassification per se, it is possible that some participants had recently changed to a more healthy diet because of early symptoms of chronic pancreatitis or because of diagnoses of other chronic illnesses (apart from cancers, which were excluded [see section 3.5 for details]). This could lead to a higher probability of being diagnosed with non-gallstone-related acute pancreatitis, either due to misclassification with chronic pancreatitis or due to positive associations with chronic illnesses (see Table 1.1 for details), whereby the HRs for healthy food items could be biased towards the null. However, as shown in Table 4.1, the main results of **Paper I–IV** did not clearly change in the sensitivity analysis in which I excluded the first 2 years of follow-up.

[76]Stability is here defined as staying in the same or an adjacent category between 1987 and 1997. Estimates were based on the women who completed the questionnaire in 1987 and that in 1997, since there is no algorithm available for the calculation of total glycemic load score from the questionnaire in 2009.
[77]Characterized by a tendency to report a low consumption of food items that are considered to be socially undesirable (and vice versa, with respect to food items that are considered to be socially desirable).

Misclassification of outcome

I relied on register-based data to define the study population in **Paper V** and to identify the outcomes of interest in **Paper I–V**, which might not have been entirely correct. However, the SNPR has been found to have a good validity for incident episodes of acute pancreatitis (PPV between 83 to 98%, irrespective of the diagnosis being primary or secondary; see section 3.4 for details) (Razavi et al., 2011), not to mention that its coverage has been complete as far back as 1985 in the studied counties (see subsection 3.1.2.1 for details). I also observed that the age- and sex-specific incidence rates in the SMC and the COSM were in good agreement with those in the Swedish population (as shown in Table 3.2). In contrast, there has been no validation of the SNPR with respect to recurrent episodes of acute pancreatitis and/or incident episodes of chronic pancreatitis. Therefore, to minimize the amount of false-positive cases in **Paper V**, I only used primary diagnosis codes and also restricted the case definition to episodes of recurrent and progressive pancreatic disease that occurred after 90 days of the incident diagnosis (because it has been reported that less than one-third of early readmissions [ie, within 30 days of discharge] are due to recurrent episodes of acute pancreatitis, whereas later readmissions are more likely to be so [Vipperla et al., 2014; Whitlock et al., 2010]).

The outcome of interest in **Paper I–IV**, that is, non-gallstone-related acute pancreatitis, might have been subject to further misclassification because of the register-based data, despite the fact that the overall percentage of non-gallstone-related acute pancreatitis (56%) was similar to that in Swedish studies relying on medical chart data (52 to 61%) (Bertilsson et al., 2015; Lindkvist et al., 2012; Razavi et al., 2011). In addition, as shown in Figure 3.3, the 2-year variation in the classification percentage of non-gallstone-related acute pancreatitis was rather low (50 to 64%). One way in which a classification error may have occurred is through underdetection of gallstones in the early diagnostics of acute pancreatitis, which could be either non-differential (with respect to diet and most other factors, because very small gallstones can sometimes go undetected [Johnson & Lévy, 2010]) or differential (with respect to obesity, because gallstones might be harder to detect in obese people than in non-obese people [Oria, 1998]). However, as shown in Table 4.1, the main results of **Paper I–IV** were not changed in the sensitivity analysis in which the cases had no history of cholelithiasis and/or gallbladder and bile duct surgeries within 3 years after the index episode. For a long time during my PhD-studies, I was certain that any outcome misclassification in **Paper I–IV** should have been non-differential with respect to diet. In hindsight, though, I must confess that it might have been a faulty assumption. Technically, the outcome was not defined as the absence of cholelithiasis and/or gallbladder and bile duct surgeries within 3 months after the index episode but rather as the absence of such diagnosis and surgery within 3 months after the index episode *or for as long as there were post-diagnosis follow-up data if the follow-up was less than 3 months*. This means that the participants who died within 90 days of the diagnosis were—by default—classified as non-gallstone-related acute pancreatitis if no investigation for gallstones had been performed. In general, and in line with the previous discussion on survival bias in subsection 5.2.1, it is reasonable that a low diet quality and a low nutritional status is associated with an increased risk of pancreatitis-related death,

which, in turn, could lead to some degree of differential outcome misclassification.[78] Taking us back to **Paper I** for a descriptive example, it might be that an erroneous overdiagnosis in participants with a low vegetable consumption biased the HR for the highest compared with the lowest quintile away from the null. To estimate the extent of such a bias, I performed a sensitivity analysis in which I assumed that the cases of non-gallstone-related acute pancreatitis were misclassified if they had died within 90 days of the diagnosis (n = 31). However, the impact on the results was very small (the multivariable-adjusted HR remained at 0.56, although the 95% CIs changed from 0.37–0.84 to 0.36–0.86). Even though I have no clear answer on how to avoid this type of bias in my future studies, at least not as long as the outcome is defined via register-based data, it is important to remember its presence and potential implications. Finally, the possibility of misclassification between acute pancreatitis and acute-on-chronic pancreatitis cannot be excluded. While I tried to account for chronic episodes that preceded acute episodes (by using chronic pancreatitis as a censoring event in the Cox regression model), I did not do so for acute episodes that preceded chronic episodes (which was rather inconsistent, since acute-on-chronic pancreatitis could very well be classified as acute pancreatitis in an early stage).[79] However, the main results of **Paper I–IV** were unaltered in sensitivity analyses in which the cases were re-classified as non-cases if there was evidence of chronic pancreatic disease within 90 days of the diagnosis. As an example, the multivariable-adjusted HR was 0.55 (95% CI, 0.37–0.83) for the highest compared with the lowest quintile of vegetable consumption (10 cases re-classified).

5.2.3.3 Confounding bias

A simple, yet elegant, definition of confounding has been given by Rothman (2012), who defines it as "confusion of effects". This means that the effect of an exposure on an outcome is mixed with the effect of another variable (a so-called confounder), which, in turn, leads to bias. A good example of confounding is the association between coffee consumption and mortality in the National Institutes of Health-AARP Diet and Health Study, a large, prospective cohort study of more than 400,000 US men and women (Freedman, Park, Abnet, Hollenbeck, & Sinha, 2012). In the crude analysis, the persons who drank the most coffee had the highest mortality rates. However, they were also more likely to smoke (6 to 7 times more likely than were non-drinkers) and, when the authors had controlled for cigarette smoking, there was actually an inverse association between coffee consumption and mortality. In order for a covariate to be considered a confounder, at least in the traditional sense, it must meet 3 specific criterions: (*i*) it must be associated with the outcome, (*ii*) it must be associated with the exposure, and (*iii*) it must not be an

[78]This could be of particular concern for obesity because of its strong association with acute pancreatitis-related mortality (Martínez et al., 2006). Hence, the exposure misclassification due to obesity (and the bias thereof) could be accompanied by an outcome misclassification that leads to further bias in the same direction.

[79]A further inconsistency was that I excluded (instead of censored) the participants who had developed pancreatic cancer during the follow-up periods of **Paper I–IV** (see subsection 3.5.1 for details), for which I have no good explanation. In retrospect (and for future consideration), it would have been more sensible to account for any between-disease misclassification in the same way, whether that had been via exclusion or via censoring (or via none of them). However, it should be noted that censoring of both diseases (HR, 0.57; 95% CI, 0.38–0.85), exclusion of both diseases (HR, 0.61; 95% CI, 0.40–0.93), and ignorance of both diseaes (HR, 0.58; 95% CI, 0.38–0.86) produced a similar association between vegetable consumption and risk of non-gallstone-related acute pancreatitis.

effect of the exposure (a so-called intermediate). The structure of the relationship between an exposure (including an intermediate step), a confounder, and an outcome is shown in Figure 5.3.

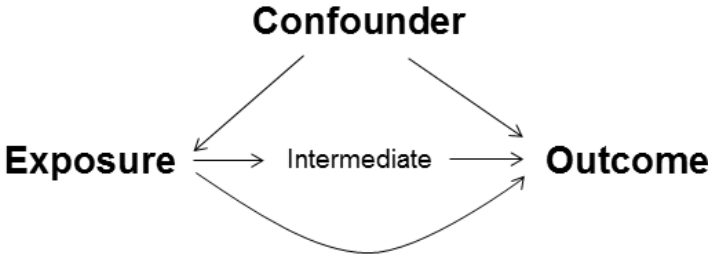

Figure 5.3: Example of the relationship between an exposure (eg, vegetable consumption), a confounder (eg, cigarette smoking), and an outcome (eg, non-gallstone-related acute pancreatitis). The intermediate step could, for example, be reduction in body weight due to the exposure.

In **Paper I–V**, I controlled for confounding by including the potential confounders into the Cox regression model, which, amongst others, included alcohol intake, cigarette smoking, and physical activity (see subsection 3.6.1.3 for full details).[80] In addition, as shown in Table 4.1, the potential intermediate role of diabetes, BMI, and hyperlipidemia in **Paper I–IV** was assessed by performing sensitivity analyses with and without these covariates (although it can be rather hard to test whether covariates are confounders or intermediates, especially when the covariates are measured only once and at the same time as the exposures).

Despite the adjustment for a large number potential confounders, which limited the overall influence of confounding bias, the possibility of residual confounding (which refers to confounding due to measurement error in, or missmodeling of, covariates) or unmeasured confounding (which refers to confounding due to covariates that are either unmeasured or difficult to measure) cannot be excluded as an explanation to the findings in **Paper I–V**.[81] However, if we go back to **Paper I** for a final example, it is hard to think of a covariate that would be so strongly correlated with both vegetable consumption and risk of non-gallstone-related acute pancreatitis that it produced a dose-response association; while, at the same time, it would not be correlated with fruit consumption. For reasons of comparability, I also tried to standardize the "between-study confounding" of **Paper I–IV** by using (*i*) a joint multivariable model (to account for residual and unmeasured confounding because of differences in the inclusion and modeling of covariates), (*ii*) attained age as time scale (to account for residual confounding because of missmodeling of age), and (*iii*) multiple imputation to handle missing data (to account for residual confounding because of incorrect handling of missing data [Knol et al., 2010]) (see Table 3.3 and Table 4.1 for details). The probability of residual confounding because of missmodeling of covariates should have been especially high in **Paper V**, since the low number of events per parameter forced me to model each covariate as a

[80]Confounding can also be addressed during the study design by randomization (only in experimental studies), matching, or restriction. An example of restriction is to only enroll women (or only men) if sex is thought to be an important confounder.

[81]For example, it had been desirable to have specific data on hypertriglyceridemia (instead of hyperlipidemia) in **Paper I–V** (Lindkvist et al., 2012; Murphy et al., 2013) as well as more clinical data on disease severity and treatment choices in **Paper V**.

one-parameter variable. Finally, in addition to any residual confounding at baseline, there were apparent changes in the participants' cigarette smoking habits between 1997 and 2009 (around 60% had stopped to smoke between the 2 questionnaires; see Table 4.3 for details), which is line with the national trend in Sweden (Patja, Hakala, Boström, Nordgren, & Haglund, 2009). The study population in **Paper V** had also changed its alcohol intake drastically following a diagnosis of non-gallstone-related acute pancreatitis (as discussed in subsection 5.1.2). It is unclear how much, if at all, such misclassification might have confounded the exposure-outcome associations in **Paper I–V**.

5.2.4 Generalizability

Generalizability refers to the extent to which the findings in a sample of a population, say, the SMC and the COSM, can be generalized to a broader population, say, the Swedish population. As shown in Table 3.1, the SMC and the COSM were representative of the Swedish population of middle-aged and elderly persons in terms of age distribution, education, BMI, and cigarette smoking. Likewise, because the incidence rates in the SMC and the COSM were highly similar to those in the Swedish population, the study population in **Paper V** is expected to be representative of any would-be study population recruited from other parts of Sweden. As such, the results of **Paper I–V** are likely to be generalizable to middle-aged and elderly Swedish persons. Whether the results are generalizable to populations with other characteristics (eg, different age structures and/or ethnic distributions) is purely speculative. However, the pursuit of representativeness (to obtain generalizable results) is less of a priority in analytical epidemiology than is the pursuit of a low degree of systematic errors (to obtain valid results)—or, to quote Rothman (2012): "[e]levating the importance of representativeness is a fallacy that has plagued epidemiologic studies for decades".

6 Final remarks

6.1 Conclusion

Based on the 5 publications that were included in this thesis, all of which were conducted in the setting of 2 large prospective cohorts of Swedish men and women, I draw the following conclusions:

- Incidence of non-gallstone-related acute pancreatitis had an inverse association with consumption of vegetables and total fish (**Paper I** and **III**), a positive association with consumption of high-glycemic load foods (**Paper II**), and a null association with consumption of fruit and coffee (**Paper I** and **IV**).
- The association between consumption of vegetables, total fish, and high-glycemic load foods and incidence of non-gallstone-related acute pancreatitis seemed to be more pronounced in persons who drank 1 or more standard drinks of alcohol per day (**Paper I–III**).
- Recurrence and progression of non-gallstone-related acute pancreatitis had no clear association with overall diet quality (calculated using a recommended food score), although the rates were lower in persons with a higher diet quality (**Paper V**).
- One-fifth of the persons who had been diagnosed with non-gallstone-related acute pancreatitis had stopped drinking alcohol in the post-diagnosis phase (**Paper V**).

Taken together, these findings suggest that a diet in line with the Swedish dietary recommendations (ie, high in vegetables and whole grains and moderate in fish) might be important in the primary prevention of non-gallstone-related acute pancreatitis. As such, the thesis uniquely contributes to the existing literature on the role of diet in health promotion and disease prevention, including that on symptomatic gallstone disease (to which I count gallstone-related acute pancreatitis). On the other hand, the findings are less supportive of an important role of diet in the secondary prevention of non-gallstone-related acute pancreatitis (ie, as a potential way to reduce recurrence and progression), at least for the overall diet quality; even though a role of individual food items and nutrients cannot be excluded.

6.2 Future research

The publications in this thesis were based on 2 prospective cohorts and are the largest and most well-conducted epidemiological studies to date on the association between diet and risk of non-gallstone-related acute pancreatitis. (This is not to say that they are without faults, though.) However, because of the limited amount of epidemiological data in general, the publications are not giving the final answer—but rather raising the question—on whether diet has a role in the development, recurrence, and progression of non-gallstone-related acute pancreatitis. Further studies of high quality are, therefore, needed to confirm or refute my findings. However, with the upcoming publication of the findings from the Multiethnic Cohort, and the positive reception that **Paper I–IV** have received from the scientific community, I am convinced that a number of studies are to follow in the near future.

One way to enhance the quality and between-study comparability of future studies is to create a unified classification of non-gallstone-related acute pancreatitis, regardless of whether it is based on health register data or medical chart data. With respect to register-based data, the chosen definition must be validated by comparing it with medical chart data. Likewise, the register-based data on recurrent episodes of acute pancreatitis and/or incident episodes of chronic pancreatitis need to be validated.

Of particular interest, at least from my personal point of view, is to expand upon the findings of **Paper V**. While the absolute implication of **Paper I–IV** is small from a public health perspective, because of the low incidence of acute pancreatitis (compared with major chronic disease, such as diabetes, cardiovascular diseases, and cancers), the relative implication of **Paper V** is substantial from a patient's perspective, because of the high risk of recurrent and progressive pancreatic disease as well as the potential impairments in quality of life and endocrine pancreatic functions. A larger sample size than what I had recruited in **Paper V** would make it possible to examine individual food items and nutrients, not the mention that access to medical charts would make it be possible to obtain data on disease severity and treatment choices, that is, clinical characteristics for which I could not properly adjust for. Ideally, the researchers should also obtain both pre-diagnosis and post-diagnosis data on diet and many other important characteristics, with the aim to determine any post-diagnosis changes and the effects thereof (especially, on the basis of my findings, on cigarette smoking and alcohol use). If such data are collected via health care providers, there is also the (theoretical) possibility to conduct a dietary intervention, which, for example, could be designed to increase consumption of vegetables and total fish, on the recurrence and progression of non-gallstone-related acute pancreatitis.

7 Acknowledgements

John Donne was undoubtedly right when he wrote that "no man is an island". I would, therefore, like to take the opportunity to thank all the people who have helped and supported me during my time as a PhD-student:

All **women** and **men** in the Swedish Mammography Cohort and the Cohort of Swedish Men, for your committed participation. I hope you realize the extent to which you have contributed, and still contribute, to the medical science.

Alicja Wolk, my main supervisor, for giving me the opportunity to be a PhD-student, for sharing your extensive knowledge in nutritional epidemiology, and for supporting me in all of my research interests and personal decisions (including that of becoming a father). It has really meant a lot.

Nicola Orsini, my co-supervisor, for always having an open door to discuss problems and questions, for sharing your life lessons, and for taking me out of my comfort zone (via travels, teaching, and statistical conferences). **Omid Sadr-Azodi**, my other co-supervisor, for introducing me to the world of research in general and to the field of acute pancreatitis in particular (actually, one could say that the last 5 years are your "fault") and for supporting me in so many ways during the years that have followed.

My colleagues, past and present, at the Unit of Nutritional Epidemiology. **Andrea Discacciati**, for having a never-ending patience to my never-ending questions; **Alice Wallin**, for being a voice of reason, telling me to calm down when I am upset about some nonsense issue; **Niclas Håkansson**, for writing the soundtrack of my (PhD) life; **Bettina Julin**, for guiding me (figuratively and literally) during my first year as a PhD-student; **Susanne Rautiainen Lagerström**, for bringing some Finnish flavor to my life; **Otto Stackelberg**, **Andrea Bellavia**, and **Alessio Crippa**, my roommates, for sharing the day-to-day office life; **Thanasis Tektonidis**, for missing a penalty shoot at the KI-cup in 2014 (as I had already done in 2013); and **Daniela Di Giuseppe**, **Agneta Åkesson**, **Holly Harris**, **JinJin Zheng Selin**, **Mimi Throne-Holst**, **Susanna Larsson**, **Nada Hana, Carolina Donat Vargas, Ann Burgaz**, **Camilla Olofsson**, and **Frej Stilling** (and everyone else who I have forgotten), for making the office such a pleasant work place.

Mina **vänner**, ingen nämnd och ingen glömd, för att ni alltid ställer upp för mig och min familj.

Mamma **Susanne** och pappa **Lars**, för att ni har stöttat och älskat mig ovillkorligt, för att ni har gett mig allt och för att ni har kämpat (och kommer att kämpa) även när det blåser snålt och gräset är grönare på andra sidan. **Frida** (och **Cristoffer**, såklart), min stora lillasyster, för att du tar hand om mig och min familj. Farmor **Gunvor** och mormor **Ulla** (som tyvärr gick bort innan jag hann avsluta mina doktorandstudier), för att ni alltid har funnits där för mig. (Och du behöver inte vara orolig, mormor, jag ska jobba som "riktig doktor" nu.) **Familjen Larsson**, för att allt ni gör för mig, er dotter/syster och ert barnbarn/syskonbarn.

Noelle, mitt mirakel, för att du har vänt upp och ner på mitt liv, för att du har lärt mig att sätta saker i perspektiv och för att jag älskar dig så mycket att jag vill Tom Cruise-hoppa i en soffa (när du har blivit så pass gammal att du kan läsa ska vi reda ut den referensen tillsammans).

Karin, min tonårskärlek, min bästa vän och min älskade fru, för att *allt* börjar och slutar med dig. Tack, tack, tack!

My PhD-studies were supported by the Swedish Research Council/Committee for Infrastructure, the Board of Research at Karolinska Institutet (Distinguished Professor Award), and the Board of Postgraduate Education at Karolinska Institutet (Clinical Scientist Training Program).

8 References

Ahlbom, A., & Alfredsson, L. (2005). Interaction: A word with two meanings creates confusion. *European Journal of Epidemiology*, *20*(7), 563-564.

Ahmed Ali, U., Issa, Y., Hagenaars, J.C., Bakker, O.J., van Goor, H., Nieuwenhuijs, V.B.,... Boermeester, M.A. (2016). Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clinical Gastroenterology and Hepatology*, *14*(5), 738-746.

Andersson, B. (2010). *Acute pancreatitis – Severity classification, complications and outcome.* (Doctoral thesis, Lund University, Lund). Retrieved 2016 February 22 from http://www.lu.se/lup/publication/1594676

Andersson, B., Appelgren, B., Sjödin, V., Ansari, D., Nilsson, J., Persson, U.,... Andersson, R. (2013). Acute pancreatitis – Costs for healthcare and loss of production. *Scandinavian Journal of Gastroenterology*, *48*(12), 1459-1465.

Ansari, D. (2014). *Pancreatic cancer – Early detection, prognostic factors, and treatment.* (Doctoral thesis, Lund University, Lund). Retrieved 2016 February 22 from http://www.lu.se/lup/publication/4643641

Appleton, K.M., Hemingway, A., Saulais, L., Dinnella, C., Monteleone, E., Depezay, L.,... Hartwell, H. (2016). Increasing vegetable intakes: Rationale and systematic review of published interventions. *European Journal of Nutrition*, *55*(3), 869-896.

Apte, M.V., Pirola, R.C., & Wilson, J.S. (2008). Individual susceptibility to alcoholic pancreatitis. *Journal of Gastroenterology and Hepatology*, *23*(Suppl 1), S63-S68.

Aune, D., Lau, R., Chan, D.S., Vieira, R., Greenwood, D.C., Kampman, E., & Norat, T. (2011). Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. *Gastroenterology*, *141*(1), 106-118.

Badalov, N., Baradarian, R., Iswara, K., Li, J., Steinberg, W., & Tenner S. (2007). Drug-induced acute pancreatitis: An evidence-based review. *Clinical Gastroenterology and Hepatology*, *5*(6), 648-661.

Baer, H.J., Glynn, R.J., Hu, F.B., Hankinson, S.E., Willett, W.C., Colditz, G.A.,... Rosner, B. (2011). Risk factors for mortality in the nurses' health study: A competing risks analysis. *American Journal of Epidemiology*, *173*(3), 319-329.

Ballard, D.D., Flueckiger, J.R., Fogel, E.L., McHenry, L., Lehman, G.A., Watkins, J.L.,... Coté, G.A. (2015). Evaluating adults with idiopathic pancreatitis for genetic predisposition: Higher prevalence of abnormal results with use of complete gene sequencing. *Pancreas*, *44*(1), 116-121.

Banks, P.A., Bollen, T.L., Dervenis, C., Gooszen, H.G., Johnson, C.D., Sarr, M.G.,... Vege, S.S. (2013). Classification of acute pancreatitis – 2012: Revision of the Atlanta classification and definitions by international consensus. *Gut*, *62*(1), 102-111.

Barlow, L., Westergren, K., Holmberg, L., & Talbäck, M. (2009). The completeness of the Swedish Cancer Register: A sample survey for year 1998. *Acta Oncologica*, *48*(1), 27-33.

Barreto, S.G. (2015). Acute pancreatitis: Watch what you eat! *American Journal of Clinical Nutrition*, *101*(5), 1097.

Bellavia, A. (2015). *A percentile approach to time-to-event outcomes.* (Doctoral thesis, Karolinska Institutet, Stockholm). Retrieved 2016 March 18 from https://openarchive.ki.se/xmlui/handle/10616/44821

Bellavia, A., Discacciati, A., Bottai, M., Wolk, A., & Orsini, N. (2015). Using Laplace regression to model and predict percentiles of age at death when age is the primary time scale. *American Journal of Epidemiology*, *182*(3), 271-277.

Bellavia, A., Larsson, S.C., Bottai, M., Wolk, A., & Orsini, N. (2013). Fruit and vegetable consumption and all-cause mortality: A dose-response analysis. *American Journal of Clinical Nutrition*, *98*(2), 454-459.

Bergström, L., Kylberg, E., Hagman, U., Erikson, H., & Bruce, Å. (1991). The food composition database KOST: The National Food Administration's Information System for nutritive values of food. *Vår Föda*, *43*(8), 439-447.

Bertilsson, S., Swärd, P., & Kalaitzakis, E. (2015). Factors that affect disease progression after first attack of acute pancreatitis. *Clinical Gastroenterology and Hepatology*, *13*(9), 1662-1669.e3.

Bexelius, T.S., Ljung, R., Mattsson, F., & Lagergren, J. (2013). Cardiovascular disease and risk of acute pancreatitis in a population-based study. *Pancreas*, *42*(6), 1011-1015.

Bhupathiraju, S.N., Tobias, D.K., Malik, V.S., Pan, A., Hruby, A., Manson, J.E.,... Hu F.B. (2014). Glycemic index, glycemic load, and risk of type 2 diabetes: Results from 3 large US cohorts and an updated meta-analysis. *American Journal of Clinical Nutrition*, *100*(1), 218-232.

Boffetta, P., McLaughlin, J.K., La Vecchia, C., Tarone, R.E., Lipworth, L., & Blot, W.J. (2008). False-positive results in cancer epidemiology: A plea for epistemological modesty. *Journal of the National Cancer Institute*, *100*(14), 988-995.

Bonn, S. (2015). *Physical activity, body mass index and prostate cancer: Studies of risk, progression and mortality.* (Doctoral thesis, Karolinska Institutet, Stockholm). Retrieved 2016 April 7 from https://openarchive.ki.se/xmlui/handle/10616/44510

Bøhn, S.K., Blomhoff, R., & Paur, I. (2014). Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. *Molecular Nutrition & Food Research*, *58*(5), 915-930.

Carter, P., Gray, L.J., Troughton, J., Khunti, K., & Davies, M.J. (2010). Fruit and vegetable intake and incidence of type 2 diabetes mellitus: Systematic review and meta-analysis. *BMJ: British Medical Journal*, *341*, c4229.

Castro-Quezada, I., Sánchez-Villegas, A., Estruch, R., Salas-Salvadó, J., Corella, D., Schröder, H.,... Serra-Majem L. (2014). A high dietary glycemic index increases total mortality in a Mediterranean population at high cardiovascular risk. *PLoS One*, *9*(9), e107968.

Cavestro, G.M., Leandro, G., Di Leo, M., Zuppardo, R.A., Morrow, O.B., Notaristefano, C.,... Testoni, P.A. (2015). A single-centre prospective, cohort study of the natural history of acute pancreatitis. *Digestive and Liver Disease*, *47*(3), 205-210.

Chang, C.C., Chiou, C.S., Lin, H.L., Wang, L.H., Chang, Y.S., & Lin, H.C. (2015). Increased risk of acute pancreatitis in patients with rheumatoid arthritis: A population-based cohort study. *PLoS One*, *10*(8), e0135187.

Chen, Y.T., Su, J.S., Tseng, C.W., Chen, C.C., Lin, C.L., & Kao, C.H. (2015). Inflammatory bowel disease on the risk of acute pancreatitis: A population-based cohort study. *Journal of Gastroenterology and Hepatology*, *31*(4), 782-787.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Cologne, J., Hsu, W.L., Abbott, R.D., Ohishi, W., Grant, E.J., Fujiwara, S., & Cullings, H.M. (2012). Proportional hazards regression in epidemiologic follow-up studies: An intuitive consideration of primary time scale. *Epidemiology*, *23*(4), 565-573.

Cox, D.R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological)*, *34*(2), 187-220.

Crippa, A., Discacciati, A., Larsson, S.C., Wolk, A., & Orsini, N. (2014). Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: A dose-response meta-analysis. *American Journal of Epidemiology*, *80*(8), 763-775

Das, S.L., Kennedy, J.I., Murphy, R., Phillips, A.R., Windsor, J.A., & Petrov, M.S. (2014). Relationship between the exocrine and endocrine pancreas after acute pancreatitis. *World Journal of Gastroenterology*, *20*(45), 17196-17205.

Das, S.L., Singh, P.P., Phillips, A.R., Murphy, R., Windsor, J.A., & Petrov, M.S. (2014). Newly diagnosed diabetes mellitus after acute pancreatitis: A systematic review and meta-analysis. *Gut*, *63*(5), 818-831.

Dawra, R., Sah, R.P., Dudeja, V., Rishi, L., Talukdar, R., Garg, P., & Saluja, A.K. (2011). Intra-acinar trypsinogen activation mediates early stages of pancreatic injury but not inflammation in mice with acute pancreatitis. *Gastroenterology*, *141*(6), 2210-2217.e2.

Delgado-Rodríguez, M., & Llorca, J. (2004). Bias. *Journal of Epidemiology and Community Health*, *58*(8), 635-641.

Di Giuseppe, D., Wallin, A., Bottai, M., Askling, J., & Wolk, A. (2014). Long-term intake of dietary long-chain n-3 polyunsaturated fatty acids and risk of rheumatoid arthritis: A prospective cohort study of women. *Annals of the Rheumatic Diseases*, *73*(11), 1949-1953.

Ding, M., Bhupathiraju, S.N., Chen, M., van Dam, R.M., & Hu F.B. (2014). Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: A systematic review and a dose-response meta-analysis. *Diabetes Care*, *37*(2), 569-586.

Ding, M., Bhupathiraju, S.N., Satija, A., van Dam, R.M., & Hu, F.B. (2014). Long-term coffee consumption and risk of cardiovascular disease: A systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation*, *129*(6), 643-659.

Ding, X., Zhang, F., & Wang, Y. (2015). Risk factors for post-ERCP pancreatitis: A systematic review and meta-analysis. *Surgeon*, *13*(4), 218-229.

Discacciati, A. (2015). *Risk factors for prostate cancer : Analysis of primary data, pooling, and related methodological aspects*. (Doctoral thesis, Karolinska Institutet, Stockholm). Retrieved 2016 March 18 from https://openarchive.ki.se/xmlui/handle/10616/44872

Discacciati, A., Orsini, N., Andersson, S.O., Andrén, O., Johansson, J.E., Mantzoros, C.S., & Wolk, A. (2013). Coffee consumption and risk of localized, advanced and fatal prostate cancer: A population-based prospective study. *Annals of Oncology*, *24*(7), 1912-1918.

Discacciati, A., Oskarsson, V., & Orsini, N. (2015). *STPHCOXRCS: Stata module to check proportional-hazards assumption using restricted cubic splines*. [Statistical component in Stata]. Retrieved 2015 October 1 from https://ideas.repec.org/c/boc/bocode/s458073.html

Djoussé, L., Akinkuolie, A.O., Wu, J.H., Ding, E.L., & Gaziano, J.M. (2012). Fish consumption, omega-3 fatty acids and risk of heart failure: A meta-analysis. *Clinical Nutrition*, *31*(6), 846-853.

Douglas, B.R., Jansen, J.B., Tham, R.T., & Lamers, C.B. (1990). Coffee stimulation of cholecystokinin release and gallbladder contraction in humans., *American Journal of Clinical Nutrition 52*(3), 553-556.

Dzeletovic, I., Harrison, M.E., Crowell, M.D., Pannala, R., Nguyen, C.C., Wu, Q., & Faigel, D.O. (2014). Pancreatitis before pancreatic cancer: Clinical features and influence on outcome. *Journal of Clinical Gastroenterology*, *48*(9), 801-805.

Eslick, G.D., Howe, P.R., Smith, C., Priest, R., & Bensoussan, A. (2009). Benefits of fish oil supplementation in hyperlipidemia: A systematic review and meta-analysis. *International Journal of Cardiology*, *136*(1), 4-16.

Feller, E.R. (1984). Endoscopic retrograde cholangiopancreatography in the diagnosis of unexplained pancreatitis. *Archives of Internal Medicine*, *144*(9), 1797-1799.

Forouzanfar, M. H., Alexander, L., Anderson, H. R., Bachman, V. F., Biryukov, S., Brauer, M.,... Ali, M. K. (2015). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, *386*(10010), 2287-2323.

Foster-Powell, K., Holt, S.H., & Brand-Miller, J.C. (2002). International table of glycemic index and glycemic load values: 2002. *American Journal of Clinical Nutrition*, *76*(1), 5-56.

Freedman, N.D., Park, Y., Abnet, C.C., Hollenbeck, A.R., & Sinha, R. (2012). Association of coffee drinking with total and cause-specific mortality. *New England Journal of Medicine*, *366*(20), 1891-1904.

Frey, C.F., Zhou, H., Harvey, D.J., & White, R.H. (2006). The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas*, *33*(4), 336-344.

Frick, T.W. (2012). The role of calcium in acute pancreatitis. *Surgery 152*(3), S157-S163.

Frossard, J.L., Steer, M.L., & Pastor, C.M. (2008). Acute pancreatitis. *Lancet*, *371*(9607), 143-152.

Gao, Y.J., Li, Y.Q., Wang, Q., Li, S.L., Li, G.Q., Ma, J.,... Wang, F.X. (2007). Analysis of clinical features of acute pancreatitis in Shandong Province, China. *Journal of Gastroenterology and Hepatology*, *22*(3), 340-344.

Girman, C.J., Kou, T.D., Cai, B., Alexander, C.M., O'Neill, E.A., Williams-Herman, D.E., & Katz, L. (2010). Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes, Obesity and Metabolism*, *12*(9), 766-771.

Gorelick, F.S., & Thrower, E. (2009). The acinar cell and early pancreatitis responses. *Clinical Gastroenterology and Hepatology*, *7*, S10-S14.

Gunnarsdottir, I., Tomasson, H., Kiely, M., Martinéz, J.A., Bandarra, N.M., Morais, M.G., & Thorsdottir, I. (2008). Inclusion of fish or fish oil in weight-loss diets for young adults: Effects on blood lipids. *International Journal of Obesity*, *32*(7), 1105-1112.

Greenland, S., Pearl, J., & Robins, J.M. (1999). Causal diagrams for epidemiologic research. *Epidemiology*, *10*(1), 37-48.

Halliwell, B., & Gutteridge, J.M.C. (2007). *Free radicals in biology and medicine* (4. ed.). New York, NY: Oxford University Press.

Harris, H., Håkansson, N., Olofsson, C., Stackelberg, O., Julin, B., Åkesson, A., & Wolk, A. (2013). The Swedish mammography cohort and the cohort of Swedish men: Study design and characteristics of two population-based longitudinal cohorts. *OA Epidemiology*, *1*(2), 16.

Hartley, L., Igbinedion, E., Holmes, J., Flowers, N., Thorogood, M., Clarke, A.,... Rees, K. (2013). Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases. *Cochrane Database of Systematic Reviews*, *6*, CD009874.

Hernán, M.A. (2010). The hazards of hazard ratios. *Epidemiology*, *21*(1), 13-15.

Hernán, M.A., Alonso, A., & Logroscino, G. (2008). Cigarette smoking and dementia: Potential selection bias in the elderly. *Epidemiology*, *19*(3), 448-450.

Jenkins, D.J., Wolever, T.M., Taylor, R.H., Barker, H., Fielden, H., Baldwin, J.M.,... Goff, D.V. (1981). Glycemic index of foods: A physiological basis for carbohydrate exchange. *American Journal of Clinical Nutrition*, *34*(3), 362-366.

Jin, J., Yu, Y.H., Zhong, M., & Zhang, G.W. (2015). Analyzing and identifying risk factors for acute pancreatitis with different etiologies in pregnancy. *Journal of Maternal-Fetal and Neonatal Medicine*, *28*(3), 267-271.

Johnson, C., & Lévy, P. (2010). Detection of gallstones in acute pancreatitis: When and how? *Pancreatology*, *10*(1), 27-32

Johnson, C.D., Besselink, M.G., & Carter, R. (2014). Acute pancreatitis. *BMJ: British Medical Journal*, *349*, g4859.

Kaluza, J., Håkansson, N., Brzozowska, A., & Wolk, A. (2009). Diet quality and mortality: A population-based prospective study of men. *European Journal of Clinical Nutrition*, *63*(4), 451-457.

Kant, A.K., Schatzkin, A., Graubard, B.I., & Schairer, C. (2000). A prospective study of diet quality and mortality in women. *JAMA: Journal of the American Medical Association*, *283*(16), 2109-2115.

Keiles, S., & Kammesheidt, A. (2006). Identification of CFTR, PRSS1, and SPINK1 mutations in 381 patients with pancreatitis. *Pancreas*, *33*(3), 221-227.

Keller, J., & Layer, P. (2005). Human pancreatic exocrine response to nutrients in health and disease. *Gut*, *54*(Suppl 6), vi1-vi28.

Klebanoff, M.A., Harper, M., Lai, Y., Thorp, J., Jr., Sorokin, Y., Varner, M.W.,... Anderson, G.D. (2011). Fish consumption, erythrocyte fatty acids, and preterm birth. *Obstetrics & Gynecology*, *117*(5), 1071-1077.

Knol, M.J., Janssen, K.J., Donders, A.R., Egberts, A.C., Heerdink, E.R., Grobbee, D.E.,... Geerlings, M.I. (2010). Unpredictable bias when using the missing indicator method or complete case analysis for missing confounder values: An empirical example. *Journal of Clinical Epidemiology*, *63*(7), 728-736.

Kolonel, L.N., Henderson, B.E., Hankin, J.H., Nomura, A.M., Wilkens, L.R., Pike, M.C.,... Nagamine, F.S. (2000). A multiethnic cohort in Hawaii and Los Angeles: Baseline characteristics. *American Journal of Epidemiology, 151*(4), 346-357

Konde, Å.B, Bjerselius, R., Haglund, L., Jansson, a., Pearson, M., Färnstrand, J.S., & Johansson, A-K. (2015). *Swedish dietary guidelines - Risk and benefit management report*. Retrieved 2016 March 10 from http://www.livsmedelsverket.se/globalassets/rapporter/2015/rapp-hanteringsrapport-engelska-omslag--inlaga--bilagor-eng-version.pdf?id=8968

Kolahdooz, F., van der Pols, J.C., Bain, C.J., Marks, G.C., Hughes, M.C., Whiteman, D.C., & Webb, P.M. (2010). Meat, fish, and ovarian cancer risk: Results from 2 Australian case-control studies, a systematic review, and meta-analysis. *American Journal of Clinical Nutrition, 91*(6), 1752-1763.

Kristiansen, L., Grønbaek, M., Becker, U., & Tolstrup, J.S. (2008). Risk of pancreatitis according to alcohol drinking habits: A population-based cohort study. *American Journal of Epidemiology, 168*(8), 932-937.

Lai, S.W., Lai, H.C., Lin, C.L., Liao, K.F., & Tseng, C.H. (2015). Chronic osteomyelitis correlates with increased risk of acute pancreatitis in a case-control study in Taiwan. *European Journal of Internal Medicine, 26*(6), 429-432.

Lankisch, P.G., Apte, M., & Banks, P.A. (2015). Acute pancreatitis. *Lancet, 386*(9988), 85-96.

Lankisch, P.G., Breuer, N., Bruns, A., Weber-Dany, B., Lowenfels, A.B., & Maisonneuve, P. (2009). Natural history of acute pancreatitis: A long-term population-based study. *American Journal of Gastroenterology, 104*(11), 2797-2805.

Lankisch, P.G., Lowenfels, A.B., & Maisonneuve, P. (2002). What is the risk of alcoholic pancreatitis in heavy drinkers? *Pancreas, 25*(4), 411-412.

Larsson, S.C., & Orsini, N. (2011). Fish consumption and the risk of stroke: A dose-response meta-analysis. *Stroke, 42*(12), 3621-3623.

Larsson, S.C., Åkesson, A., & Wolk, A. (2014). Overall diet quality and risk of stroke: A prospective cohort study in women. *Atherosclerosis, 233*(1), 27-29.

Leitzmann, M.F., Giovannucci, E.L., Stampfer, M.J., Spiegelman, D., Colditz, G.A., Willett, W.C., & Rimm, E.B. (1999). Prospective study of alcohol consumption patterns in relation to symptomatic gallstone disease in men. *Alcoholism: Clinical and Experimental Research, 23*(5), 835-841.

Leitzmann, M.F., Stampfer, M.J., Willett, W.C., Spiegelman, D., Colditz, G.A., & Giovannucci, E.L. (2002). Coffee intake is associated with lower risk of symptomatic gallstone disease in women. *Gastroenterology, 123*(6), 1823-1830.

Leitzmann, M.F., Tsai, C.J., Stampfer, M.J., Rimm, E.B., Colditz, G.A., Willett, W.C., & Giovannucci, E.L. (2003). Alcohol consumption in relation to risk of cholecystectomy in women. *American Journal of Clinical Nutrition, 78*(2), 339-347.

Leitzmann, M.F., Willett, W.C., Rimm, E.B., Stampfer, M.J., Spiegelman, D., Colditz, G.A., & Giovannucci, E. (1999). A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. *JAMA: Journal of the American Medical Association, 281*(22), 2106-2112.

Leung, P.S., & Chan, Y.C. (2009). Role of oxidative stress in pancreatic inflammation. *Antioxidants & Redox Signaling, 11*(1), 135-165.

Levitan, E.B., Cook, N.R., Stampfer, M.J., Ridker, P.M., Rexrode, K.M., Buring, J.E.,... Liu, S. (2008). Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. *Metabolism, 57*(3), 437-443.

Levitan, E.B., Westgren, C.W., Liu, S., & Wolk, A. (2007). Reproducibility and validity of dietary glycemic index, dietary glycemic load, and total carbohydrate intake in 141 Swedish men. *American Journal of Clinical Nutrition, 85*(2), 548-553.

Lindkvist, B., Appelros, S., Manjer, J., & Borgström, A. (2004). Trends in incidence of acute pancreatitis in a Swedish population: Is there really an increase? *Clinical Gastroenterology and Hepatology, 2*(9), 831-837.

Lindkvist, B., Appelros, S., Manjer, J., Berglund, G., & Borgstrom, A. (2008). A prospective cohort study of smoking in acute pancreatitis. *Pancreatology, 8*(1), 63-70.

Lindkvist, B., Appelros, S., Regnér, S., & Manjer, J. (2012). A prospective cohort study on risk of acute pancreatitis related to serum triglycerides, cholesterol and fasting glucose. *Pancreatology, 12*(4), 317-324.

Ljung, R., Lagergren, J., Bexelius, T.S., Mattsson, F., & Lindblad, M. (2012). Increased risk of acute pancreatitis among tetracycline users in a Swedish population-based case-control study. *Gut, 61*(6), 873-876.

Ludvigsson, J.F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.L., Reuterwall, C.,... Olausson, P.O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health, 11*, 450.

Ludvigsson, J.F., Otterblad-Olausson, P., Pettersson, B.U., & Ekbom, A. (2009). The Swedish personal identity number: Possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology, 24*(11), 659-667.

Lunet, N., Lacerda-Vieira, A., & Barros, H. (2005). Fruit and vegetables consumption and gastric cancer: A systematic review and meta-analysis of cohort studies. *Nutrition and Cancer, 53*(1), 1-10.

Martínez, J., Johnson, C.D., Sánchez-Payá, J., de Madaria, E., Robles-Díaz, G., & Pérez-Mateo, M. (2006). Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: An updated meta-analysis. *Pancreatology, 6*(3), 206-209.

Matteo, A., & Sarles, H. (1990). Is food allergy a cause of acute pancreatitis? *Pancreas, 5*(2), 234-237.

McCullough, M.L., Feskanich, D., Stampfer, M.J., Giovannucci, E.L., Rimm,E.B., Hu, F.B.,... Willett, W.C. (2002). Diet quality and major chronic disease risk in men and women: Moving toward improved dietary guidance. *American Journal of Clinical Nutrition, 76*(6), 1261-1271.

Mendez, M.A., Popkin, B.M., Buckland, G., Schroder, H., Amiano, P., Barricarte, A.,... González, C.A. (2011). Alternative methods of accounting for underreporting and overreporting when measuring dietary intake-obesity relations. *American Journal of Epidemiology, 173*(4), 448-458.

Messerer, M., Håkansson, N., Wolk, A., & Åkesson, A. (2008). Dietary supplement use and mortality in a cohort of Swedish men. *British Journal of Nutrition, 99*(3), 626-631.

Michels, K.B., & Wolk, A. (2002). A prospective study of variety of healthy foods and mortality in women. *International Journal of Epidemiology, 31*(4), 847-854.

Mirrahimi, A., Chiavaroli, L., Srichaikul, K., Augustin, L.S., Sievenpiper, J.L., Kendall, C.W., & Jenkins, D.J. (2014). The role of glycemic index and glycemic load in cardiovascular disease and its risk factors: a review of the recent literature. *Current Atherosclerosis Reports*, *16*(1), 381.

Mitta, N., Barreto, S.G., & Rodrigues, J. (2011). Dietary risk factors for acute pancreatitis: A case-control study. *Surgical Chronicles*, *16*(3), 186-187.

Morinville, V.D., Barmada, M.M., & Lowe, M.E. (2010). Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: Is greater awareness among physicians responsible? *Pancreas*, *39*(1), 5-8.

Morton, C., Klatsky, A.L., & Udaltsova, N. (2004). Smoking, coffee, and pancreatitis. *American Journal of Gastroenterology*, *99*(4), 731-738.

Murakami, K., McCaffrey, T.A., & Livingstone, M.B. (2013). Associations of dietary glycaemic index and glycaemic load with food and nutrient intake and general and central obesity in British adults. *British Journal of Nutrition*, *110*(11), 2047-2057.

Murphy, M.J., Sheng, X., MacDonald, T.M., & Wei, L. (2013). Hypertriglyceridemia and acute pancreatitis. *JAMA Internal Medicine*, *173*(2), 162-164.

Natella, F., & Scaccini, C. (2012). Role of coffee in modulation of diabetes risk. *Nutrition Reviews*, *70*(4), 207-217.

Nationella Diabetesregistret (NDR) – Registercentrum Västra Götaland. (2014). *Årsrapport. 2014 års resultat*. Retrieved 2016 March 15 from https://www.ndr.nu/pdfs/Arsrapport_NDR_2014.pdf.

Niederau, M., Niederau, C., & Strohmeyer, G. (1988). Epidemiology of acute pancreatitis: Mortality data and correlation to consumption of alcohol and dietary factors. [Conference abstract]. *Digestion*, *40*(2), 104-105.

Noel, R.A., Braun, D.K., Patterson, R.E., & Bloomgren, G.L. (2009). Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: A retrospective cohort study. *Diabetes Care*, *32*(5), 834-838.

Nordback, I., Pelli, H., Lappalainen-Lehto, R., Järvinen, S., Räty, S., & Sand, J. (2009). The recurrence of acute alcohol-associated pancreatitis can be reduced: A randomized controlled trial. *Gastroenterology*, *136*(3), 848-855.

Nordenvall, C., Oskarsson, V., & Wolk, A. (2015). Inverse association between coffee consumption and risk of cholecystectomy in women but not in men. *Clinical Gastroenterology and Hepatology*, *13*(6), 1096-1102.e1.

Nordenvall, C., Oskarsson, V., & Wolk, A. (2016). Fruit and vegetable consumption and risk of cholecystectomy: A prospective cohort study of women and men. *Submitted manuscript.*

O'Keefe, J.H., Bhatti, S.K., Patil, H.R., DiNicolantonio, J.J., Lucan, S.C., & Lavie, C.J. (2013). Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. *Journal of the American College of Cardiology*, *62*(12), 1043-1051.

Oskarsson, V. (2015). *The use of restricted cubic splines to evaluate nonproportional hazards in Cox regression* [PowerPoint presentation]. Retrieved 2016 March 25 from http://www.stata.com/meeting/nordic-and-baltic15/abstracts/materials/sweden15_oskarsson.pdf

Oskarsson, V., Mehrabi, M., Orsini, N., Hammarqvist, F., Segersvärd, R., Andrén-Sandberg, Å., & Sadr-Azodi, O. (2011). Validation of the harmless acute pancreatitis score in predicting nonsevere course of acute pancreatitis. *Pancreatology, 11*(5), 464-468.

Oskarsson, V., Orsini, N., Sadr-Azodi, O., & Wolk, A. (2014). Postmenopausal hormone replacement therapy and risk of acute pancreatitis: A prospective cohort study. *CMAJ: Canadian Medical Association Journal, 186*(5), 338-344.

Oria, H.E. (1998). Pitfalls in the diagnosis of gallbladder disease in clinically severe obesity. *Obesity Surgery, 8*(4), 444-451.

Orsini, N., & Greenland, S. (2011). A procedure to tabulate and plot results after flexible modeling of quantitative covariate. *Stata Journal, 11*(1), 1-29.

Pandol, S.J., Lugea, A., Mareninova, O.A., Smoot, D., Gorelick, F.S., Gukovskaya, A.S., & Gukovsky, I. (2011). Investigating the pathobiology of alcoholic pancreatitis. *Alcoholism: Clinical and Experimental Research, 35*(5), 830-837.

Patel, R.S., Johlin, F.C., Jr., & Murray, J.A. (1999). Celiac disease and recurrent pancreatitis. *Gastrointestinal Endoscopy, 50*(6), 823-827.

Patja, K., Hakala, S.M., Boström, G., Nordgren, P., & Haglund, M. (2009). Trends of tobacco use in Sweden and Finland: Do differences in tobacco policy relate to tobacco use? *Scandinavian Journal of Public Health, 37*(2), 153-160.

Peery, A.F., Dellon, E.S., Lund, J., Crockett, S.D., McGowan, C.E., Bulsiewicz, W.J.,... Shaheen, N.J. (2012). Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology, 143*(5), 1179-1187.e1-3.

Pelli, H., Lappalainen-Lehto, R., Piironen, A., Sand, J., & Nordback, I. (2008). Risk factors for recurrent acute alcohol-associated pancreatitis: A prospective analysis. *Scandinavian Journal of Gastroenterology, 43*(5), 614-621.

Pendharkar, S.A., Salt, K., Plank, L.D., Windsor, J.A., & Petrov, M.S. (2014). Quality of life after acute pancreatitis: A systematic review and meta-analysis. *Pancreas, 43*(8), 1194-1200

Petrov, M.S., Shanbhag, S., Chakraborty, M., Phillips, A.R., & Windsor, J.A. (2010). Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology, 139*(3), 813-820.

Portincasa, P., Moschetta, A., & Palasciano, G. (2006). Cholesterol gallstone disease. *Lancet, 368*(9531), 230-239.

Prizment, A.E., Jensen, E.H., Hopper, A.M., Virnig, B.A., & Anderson, K.E. (2015). Risk factors for pancreatitis in older women: The Iowa Women's Health Study. *Annals of Epidemiology, 25*(7), 544-548.

Rakonczay, Z., Jr., Hegyi, P., Takács, T., McCarroll, J., & Saluja, A.K. (2008). The role of NF-kappaB activation in the pathogenesis of acute pancreatitis. *Gut, 57*(2), 259-267.

Rautiainen Lagerström, S. (2012). *Antioxidants from diet and supplements in relation to cardiovascular disease*. (Doctoral thesis, Karolinska Institutet, Stockholm). Retrieved 2016 April 10 from https://openarchive.ki.se/xmlui/handle/10616/41043

Razavi, D., Ljung, R., Lu, Y., Andrén-Sandberg, Å., & Lindblad, M. (2011). Reliability of acute pancreatitis diagnosis coding in a National Patient Register: A validation study in Sweden. *Pancreatology*, *11*(5), 525-532.

Rebello, S.A., & van Dam, R.M. (2013). Coffee consumption and cardiovascular health: Getting to the heart of the matter. *Current Cardiology Reports*, *15*(10), 403.

Rice, T.K., Schork, N.J., & Rao, D.C. (2008). Methods for handling multiple testing. *Advances in Genetics*, *60*, 293-308.

Rix, T.A., Joensen, A.M., Riahi, S., Lundbye-Christensen, S., Tjønneland, A., Schmidt, E.B., & Overvad, K. (2014). A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter – A Danish cohort study. *Europace*, *16*(11), 1554-1561.

Rothman, K.J. (2002). *Episheet: Spreadsheets for the analysis of epidemiologic data*. [Statistical software]. Retrieved 2016 April 14 from http://www.krothman.org/episheet.xls

Rothman, K.J. (2012). *Epidemiology: An introduction* (2. ed.). New York, NY: Oxford University Press.

Rothman, K.J., Greenland, S., & Lash, T.L. (2008). *Modern epidemiology* (3. ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Royston, P., & Lambert, P.C. (2011). *Flexible parametric survival analysis using Stata: Beyond the Cox model* (1. ed.). College Station, TX: Stata Press.

Sadr-Azodi, O., Andrén-Sandberg, Å., Orsini, N., & Wolk, A. (2012). Cigarette smoking, smoking cessation and acute pancreatitis: A prospective population-based study. *Gut*, *61*(2), 262-267.

Sadr-Azodi, O., Mattsson, F., Bexlius, T.S., Lindblad, M., Lagergren, J., & Ljung, R. (2013). Association of oral glucocorticoid use with an increased risk of acute pancreatitis: A population-based nested case-control study. *JAMA Internal Medicine*, *173*(6), 444-449.

Sadr-Azodi, O., Orsini, N., Andrén-Sandberg, Å., & Wolk, A. (2011). Effect of type of alcoholic beverage in causing acute pancreatitis. *British Journal of Surgery*, *98*(11), 1609-1616.

Sadr-Azodi, O., Orsini, N., Andrén-Sandberg, Å., & Wolk, A. (2013). Abdominal and total adiposity and the risk of acute pancreatitis: A population-based prospective cohort study. *American Journal of Gastroenterology*, *108*(1), 133-139.

Sadr-Azodi, O., Sanders, D.S., Murray, J.A., & Ludvigsson, J.F. (2012). Patients with celiac disease have an increased risk for pancreatitis. *Clinical Gastroenterology and Hepatology*, *10*(10), 1136-1142.e3.

Sah, R.P., Dawra, R.K., & Saluja, A.K. (2013). New insights into the pathogenesis of pancreatitis. *Current Opinion In Gastroenterology*, *29*(5), 523-530.

Sah, R.P., & Saluja, A. (2011). Molecular mechanisms of pancreatic injury. *Current Opinion In Gastroenterology*, *27*(5), 444-451.

Salmeron, J., Manson, J.E., Stampfer, M.J., Colditz, G.A., Wing, A.L., & Willett, W.C. (1997). Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA: Journal of the American Medical Association*, *277*(6), 472-477.

Saluja, A.K., Lerch, M.M., Phillips, P.A., & Dudeja, V. (2007). Why does pancreatic overstimulation cause pancreatitis? *Annual Review of Physiology*, *69*, 249-269.

Samokhvalov, A.V., Rehm, J., & Roerecke, M. (2015). Alcohol consumption as a risk factor for acute and chronic pancreatitis: A systematic review and a series of meta-analyses. *EBioMedicine*, *2*(12), 1996-2002.

Sandhu, S., Al-Sarraf, A., Taraboanta, C., Frohlich, J., & Francis, G.A. (2011). Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe hypertriglyceridemia: A retrospective cohort study. *Lipids in Health and Disease*, *10*, 157.

Sandzén, B., Rosenmüller, M., Haapamäki, M.M., Nilsson, E., Stenlund, H.C., & Oman, M. (2009). First attack of acute pancreatitis in Sweden 1988 - 2003: Incidence, aetiological classification, procedures and mortality - A register study. *BMC Gastroenterology*, *5*(9), 18.

Sankaran, S.J., Xiao, A.Y., Wu, L.M., Windsor, J.A., Forsmark, C.E., & Petrov, M.S. (2015). Frequency of progression from acute to chronic pancreatitis and risk factors: A meta-analysis. *Gastroenterology*, *149*(6), 1490-1500.e1.

Sarles, H. (1973). An international survey on nutrition and pancreatitis. *Digestion*, *9*(5), 389-403.

Sarles, H., Sarles, J.C., Camatte, R., Muratore, R., Gaini, M., Guien, C.,... Le Roy, F. (1965). Observations on 205 confirmed cases of acute pancreatitis, recurring pancreatitis, and chronic pancreatitis. *Gut*, *6*(6), 545-559.

Schmidt, D.N. (1991). Apparent risk factors for chronic and acute pancreatitis in Stockholm county. Spirits but not wine and beer. *International Journal of Pancreatology*, *8*(1), 45-50.

Schoenfeld, D. (1980). Chi-squared goodness-of-fit tests for proportional hazards regression model. *Biometrika*, *67*(1), 145-153.

Segal, I., Charalambides, D., Becker, P., & Ally, R. (2000). Case control study of environmental factors in the etiology of the first attack of acute pancreatitis: A pilot study. *International Journal of Pancreatology*, *28*(3), 169-173.

Setiawan, V.W., Pandol, S.J., Porcel, J., Wilkens, L.R., Le Marchand, L., Pike, M.C., & Monroe, K.R. (2015). Prospective study of diabetes, smoking, diet and risk of pancreatitis: The multiethnic cohort. [Conference abstract]. *Pancreas*, *44*(8), 1413-1413.

Socialstyrelsens statistikdatabas. (2016). *Diagnoser i sluten vård*. Retrieved 2016 March 7 from http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard

Stackelberg, O. (in press). *Lifestyle and risk of abdominal aortic aneurysm*. (Doctoral thesis, Karolinska Institutet, Stockholm).

Statistiska centralbyråns statistikdatabas. (2016a). *Flyttningar efter region, ålder och kön. År 1997 - 2015*. Retrieved 2016 April 11 from http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__BE__ BE-0101__BE0101J/Flyttningar97/table/tableViewLayout1/?rxid=de93af84-6468-4e2f-9a3b-262abada61f6

Statistiska centralbyråns statistikdatabas. (2016b). *Folkmängden efter region, civilstånd, ålder och kön. År 1968 - 2015*. Retrieved 2016 April 11 from http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/ START__BE__BE-0101__BE0101A/BefolkningNy/table/tableViewLayout1/?rxid=052e8995-ba1b-438e-a142-36ed1a2591b1

Sun, X., Huang, X., Zhao, R., Chen, B., & Xie, Q. (2015). Meta-analysis: Tobacco smoking may enhance the risk of acute pancreatitis. *Pancreatology, 15*(3), 286-294.

Swaroop, V.S., Chari, S.T., & Clain, J.E. (2004). Severe acute pancreatitis. *JAMA: Journal of the American Medical Association, 291*(23), 2865-2868.

Tenner, S., Baillie, J., DeWitt, J., & Vege, S.S. (2013). American College of Gastroenterology guideline: Management of acute pancreatitis. *American Journal of Gastroenterology, 108*(9), 1400-1415.

Thiébaut, A.C., & Bénichou, J. (2004). Choice of time-scale in Cox's model analysis of epidemiologic cohort data: A simulation study. *Statistics in Medicine, 23*(24), 3803-3820.

Thomas, T., Mah, L., & Barreto, S.G. (2012). Systematic review of diet in the pathogenesis of acute pancreatitis: A tale of too much or too little? *Saudi Journal of Gastroenterology, 18*(5), 310-315.

Tolles, J., & Lewis, R.J. (2016). Time-to-event analysis. *JAMA: Journal of the American Medical Association, 315*(10), 1046-1047.

Tsai, C.J., Leitzmann, M.F., Willett, W.C., & Giovannucci, E.L. (2005a). Dietary carbohydrates and glycaemic load and the incidence of symptomatic gall stone disease in men. *Gut, 54*(6), 823-828.

Tsai, C.J., Leitzmann, M.F., Willett, W.C., & Giovannucci, E.L. (2005b). Glycemic load, glycemic index, and carbohydrate intake in relation to risk of cholecystectomy in women. *Gastroenterology, 129*(1), 105-112.

Tsai, C.J., Leitzmann, M.F., Willett, W.C., & Giovannucci, E.L. (2006). Fruit and vegetable consumption and risk of cholecystectomy in women. *American Journal of Medicine, 119*(9), 760-767.

Turati, F., Galeone, C., Gandini, S., Augustin, L.S., Jenkins, D.J., Pelucchi, C., & La Vecchia, C. (2015). High glycemic index and glycemic load are associated with moderately increased cancer risk. *Molecular Nutrition & Food Research, 59*(7),1384-1394.

UK Working Party on Acute Pancreatitis. (2005). UK guidelines for the management of acute pancreatitis. *Gut, 54*, S1-S9.

van Bakel, M.M., Kaaks, R., Feskens, E.J., Rohrmann, S., Welch, A.A., Pala, V.,... Slimani, N. (2009). Dietary glycaemic index and glycaemic load in the European Prospective Investigation into Cancer and Nutrition. *European Journal of Clinical Nutrition, 63*(Suppl 4),S188-S205.

Vanderweele, T.J., & Ogburn, E.L. (2012). Theorems, proofs, examples, and rules in the practice of epidemiology. *Epidemiology, 23*(3), 443-445.

Vipperla, K., Papachristou, G.I., Easler, J., Muddana, V., Slivka, A., Whitcomb, D.C., & Yadav, D. (2014). Risk of and factors associated with readmission after a sentinel attack of acute pancreatitis. *Clinical Gastroenterology and Hepatology, 12*(11), 1911-1919.

Vittinghoff, E., & McCulloch, C.E. (2007). Relaxing the rule of ten events per variable in logistic and Cox regression. *American Journal of Epidemiology, 165*(6), 710-718.

Waldthaler, A., Schütte, K., & Malfertheiner, P. (2010). Causes and mechanisms in acute pancreatitis. *Digestive Diseases, 28*(2), 364-372.

Wallin, A. (2016). *Fish consumption in relation to type 2 diabetes and cardiovascular complications*. (Doctoral thesis, Karolinska Institutet, Stockholm). Retrieved 2016 April 8 from https://openarchive.ki.se/xmlui/handle/10616/45034

Westling, F. (2012). *Svenskar bosatta utomlands*. Retrieved 2016 April 11 from http://utbildning.gu.se/digitalAssets/1373/1373789_svenskar-bosatta-utomlands.pdf

White, I.R., Royston, P., & Wood, A.M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine*, *30*(4), 377-399.

Whitlock, T.L., Repas, K., Tignor, A., Conwell, D., Singh, V., Banks, P.A., & Wu, B.U. (2010). Early readmission in acute pancreatitis: Incidence and risk factors. *American Journal of Gastroenterology*, *105*(11), 2492-2497.

Willett, W.C. (2013). *Nutritional epidemiology* (3. ed.). New York, NY: Oxford University Press.

Wilson, J.S., Bernstein, L., McDonald, C., Tait, A., McNeil, D., & Pirola, R.C. (1985). Diet and drinking habits in relation to the development of alcoholic pancreatitis. *Gut*, *26*(9), 882-887.

Wilson, J.S., & Pirola, R.C. (1986). Diet and drinking habits in alcoholic pancreatitis: Reply. *Gut*, *27*(5), 590.

Wolk, A. (1992). [Validation of food-frequency questionnaires]. *Unpublished raw data*.

Wolk, A. (n.d.). [Validation of food-frequency questionnaires]. *Unpublished raw data*.

Working Group IAP/APA Acute Pancreatitis Guidelines. (2013). IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*, *13*(4 Suppl 2), e1-e15.

World Health Organization. (2016). *International Classification of Diseases (ICD)*. Retrieved 2016 February 26 from http://www.who.int/classifications/icd/en/

Yadav, D., & Lowenfels, A.B. (2006). Trends in the epidemiology of the first attack of acute pancreatitis: A systematic review. *Pancreas*, *33*(4), 323-330.

Yadav, D., & Lowenfels, A.B. (2013). The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*, *144*(6), 1252-1261.

Yadav, D., O'Connell, M., & Papachristou, G.I. (2012). Natural history following the first attack of acute pancreatitis. *American Journal of Gastroenterology*, *107*(7), 1096-1103.

Yang, A.L., Vadhavkar, S., Singh, G., & Omary, M.B. (2008). Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Archives of Internal Medicine*, *168*(6), 649-656.

Yang, H., Wang, L., Shi, Y.H., Sui, G.T., Wu, Y.F., Lu, X.Q.,... Qian, J.M. (2014). Risk factors of acute pancreatitis in the elderly Chinese population: A population-based cross-sectional study. *Journal of Digestive Diseases*, *15*(9), 501-507.

Yang, L., He, Z., Tang, X., & Liu, J. (2013). Type 2 diabetes mellitus and the risk of acute pancreatitis: A meta-analysis. *European Journal of Gastroenterology and Hepatology*, *25*(2), 225-231.

Yu, X.F., Zou, J., & Dong, J. (2014). Fish consumption and risk of gastrointestinal cancers: A meta-analysis of cohort studies. *World Journal of Gastroenterology*, *20*(41), 15398-15412.

Yuan, C., Lee, H.J., Shin, H.J., Stampfer, M.J., & Cho, E. (2015). Fruit and vegetable consumption and hypertriglyceridemia: Korean National Health and Nutrition Examination Surveys (KNHANES) 2007-2009. *European Journal of Clinical Nutrition, 69*(11), 1193-1199.

Zhao, L.G., Sun, J.W., Yang, Y., Ma, X., Wang, Y.Y., & Xiang, Y.B. (2016). Fish consumption and all-cause mortality: A meta-analysis of cohort studies. *European Journal of Clinical Nutrition, 70*(2), 155-161.

Zheng, J., Huang, T., Yu, Y., Hu, X., Yang, B., & Li, D. (2012). Fish consumption and CHD mortality: An updated meta-analysis of seventeen cohort studies. *Public Health Nutrition, 15*(4), 725-737.

Zyromski, N.J., Sandoval, J.A., Pitt, H.A., Ladd, A.P., Fogel, E.L., Mattar, W.E.,... Grosfeld, J.L. (2008). Annular pancreas: Dramatic differences between children and adults. *Journal of the American College of Surgeons, 206*(5), 1019-1025.

9 Supplementary material

9.1 References used in Figure 1.3

Bertilsson, S., Swärd, P., & Kalaitzakis, E. (2015). Factors that affect disease progression after first attack of acute pancreatitis. *Clinical Gastroenterology and Hepatology*, *13*(9), 1662-1669.e3.

Lindkvist, B., Appelros, S., Regnér, S., & Manjer, J. (2012). A prospective cohort study on risk of acute pancreatitis related to serum triglycerides, cholesterol and fasting glucose. *Pancreatology*, *12*(4), 317-324.

Razavi, D., Ljung, R., Lu, Y., Andrén-Sandberg, Å., & Lindblad, M. (2011). Reliability of acute pancreatitis diagnosis coding in a National Patient Register: A validation study in Sweden. *Pancreatology*, *11*(5), 525-532.

9.2 References used in Figure 1.4

Publications that were included in Figure 1.4 are listed below. In the case of several publications from the same country, I chose the one that was most relevant in terms of publication date, study size, or definition of incident acute pancreatitis.

Floyd, A., Pedersen, L., Nielsen, G.L., Thorladcius-Ussing, O., & Sorensen, H.T. (2002). Secular trends in incidence and 30-day case fatality of acute pancreatitis in North Jutland County, Denmark: A register-based study from 1981-2000. *Scandinavian Journal of Gastroenterology*, *37*(12), 1461-1465.

Frey, C.F., Zhou, H., Harvey, D.J., & White, R.H. (2006). The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas*, *33*(4), 336-344.

Głuszek, S., & Kozieł, D. (2012). Prevalence and progression of acute pancreatitis in the Świętokrzyskie Voivodeship population. *Polski Przeglad Chirurgiczny*, *84*(12), 618-625.

Hamada, S., Masamune, A., Kikuta, K., Hirota, M., Tsuji, I., & Shimosegawa, T. (2014). Nationwide epidemiological survey of acute pancreatitis in Japan. *Pancreas*, *43*(8), 1244-1248.

Jaakkola, M., & Nordback, I. (1993). Pancreatitis in Finland between 1970 and 1989. *Gut*, *34*(9), 1255-1260.

Lankisch, P.G., Karimi, M., Bruns, A., Maisonneuve, P., & Lowenfels, A.B. (2009). Temporal trends in incidence and severity of acute pancreatitis in Lüneburg County, Germany: A population-based study. *Pancreatology*, *9*(4), 420-426.

McKay, C.J., Evans, S., Sinclair, M., Carter, C.R., & Imrie, C.W. (1999). High early mortality rate from acute pancreatitis in Scotland, 1984-1995. *British Journal of Surgery*, *86*(10), 1302-1305.

Méndez-Bailón, M., de Miguel Yanes, J.M., Jiménez-García, R., Hernández-Barrera, V., Pérez-Farinós, N., & López-de-Andrés, A. (2015). National trends in incidence and outcomes of acute pancreatitis among type 2 diabetics and non-diabetics in Spain (2001-2011). *Pancreatology*, *15*(1), 64-70.

O'Farrell, A., Allwright, S., Toomey, D., Bedford, D., & Conlon, K. (2007). Hospital admission for acute pancreatitis in the Irish population, 1997 2004: Could the increase be due to an increase in alcohol-related pancreatitis? *Journal of Public Health (Oxford Journals)*, *29*(4), 398-404.

Omdal, T., Dale, J., Lie, S.A., Iversen, K.B., Flaatten, H., & Ovrebo, K. (2011). Time trends in incidence, etiology, and case fatality rate of the first attack of acute pancreatitis. *Scandinavian Journal of Gastroenterology*, *46*(11), 1389-1398.

Roberts, S.E., Williams, J.G., Meddings, D., & Goldacre, M.J. (2008). Incidence and case fatality for acute pancreatitis in England: Geographical variation, social deprivation, alcohol consumption and aetiology – A record linkage study. *Alimentary Pharmacology & Therapeutics*, *28*(7), 931-941.

Roberts, S.E., Akbari, A., Thorne, K., Atkinson, M., & Evans, P.A. (2013). The incidence of acute pancreatitis: Impact of social deprivation, alcohol consumption, seasonal and demographic factors. *Alimentary Pharmacology & Therapeutics*, *38*(5), 539-548.

Sandzén, B., Rosenmüller, M., Haapamäki, M.M., Nilsson, E., Stenlund, H.C., & Oman, M. (2009). First attack of acute pancreatitis in Sweden 1988 - 2003: Incidence, aetiological classification, procedures and mortality - A register study. *BMC Gastroenterology*, *5*(9), 18.

Shen, H.N., Lu, C.L., & Li, C.Y. (2012). Epidemiology of first-attack acute pancreatitis in Taiwan from 2000 through 2009: A nationwide population-based study. *Pancreas*, *41*(5), 696-702.

Spanier, B., Bruno, M.J., & Dijkgraaf, M.G. (2013). Incidence and mortality of acute and chronic pancreatitis in the Netherlands: A nationwide record-linked cohort study for the years 1995-2005. *World Journal of Gastroenterology*, *19*(20), 3018-3026.

Stimac, D., Mikolasevic, I., Krznaric-Zrnic, I., Radic, M., & Milic, S. (2013). Epidemiology of acute pancreatitis in the North Adriatic region of Croatia during the last ten years. *Gastroenterology Research and Practice*, *2013*, 956149.

Vidarsdottir, H., Möller, P.H., Vidarsdottir, H., Thorarinsdottir, H., & Björnsson, ES. (2013). Acute pancreatitis: A prospective study on incidence, etiology, and outcome. *European Journal of Gastroenterology & Hepatology*, *25*(9), 1068-1075.

9.3 Table S.1

Table S.1: Cox regression-derived HRs of gallstone-related acute pancreatitis and cholecystectomy according to a number of modifiable risk factors, 1998 to 2011*

	Gallstone-related acute pancreatitis (*N* = 81,365; *n* = 313)†	**Cholecystectomy (*N* = 76,034; *n* = 2207)‡**
Risk factor	**HR (95% CI)§**	**HR (95% CI)¶**
Cigarette smoking (current vs. never)	0.94 (0.67–1.31)	1.02 (0.91–1.15)
Alcohol intake‖ (≥1 vs. <1 drink/day)	0.70 (0.51–0.96)	0.81 (0.73–0.91)
BMI (≥30 vs. <25 kg/m^2)	1.82 (1.28–2.58)	1.76 (1.54–2.02)
Physical activity¥ (>40 vs. <20 min/day)	0.86 (0.65–1.13)	0.85 (0.76–0.94)
Vegetable consumption (highest vs. lowest quartile)	0.93 (0.66–1.31)	0.96 (0.84–1.09)
Glycemic load score (highest vs. lowest quartile)	1.41 (1.01–1.98)	1.23 (1.09–1.39)
Fish consumption (>3.0 vs. <1 serving/day)	0.93 (0.64–1.35)	1.02 (0.88–1.19)
Coffee consumption (≥5 vs. <2 cups/day)	0.63 (0.42–0.93)	0.77 (0.66–0.89)

BMI, body mass index; CI, confidence interval; COSM, Cohort of Swedish Men; HR, hazard ratio; SMC, Swedish Mammography Cohort.

*At the time of this analysis (20150530), I only had data on cholecystectomy through 2011.

†*N* equals the number of participants in the SMC and the COSM who, at baseline, were free of pancreatic diseases and cancer and had plausible energy intakes (≤3 standard deviations of the sex-specific log-transformed mean); *n* equals the number of cases of gallstone-related acute pancreatitis during the follow-up period.

‡*N* equals the number of participants in the SMC and the COSM who, at baseline, were free of cholecystectomy and cancer and had plausible energy intakes (defined as above); *n* equals the number of cases of cholecystectomy during follow-up period.

§Follow-up time was censored at the date of non-malignant pancreatic disease, death, or December 31, 2011, whichever came first. Estimates were adjusted for age (time scale), sex, cigarette smoking (never, former, current), alcohol drinking (never and former, <1, ≥1 drink/day), BMI (<25, 25–29, ≥30 kg/m^2), physical activity (<20, 20–40, >40 min/day), vegetable consumption (quartiles of servings/day), glycemic load (quartiles of score/day), fish consumption (<1.0, 1.0–1.9, 2.0–3.0, >3.0 servings/week), coffee consumption (<2, 2, 3–4, ≥5 cups/day), and energy intake (sex-specific quartiles of kcal/day).

¶Follow-up time was censored at the date cholecystectomy, death, or December 31, 2011, whichever came first. Estimates were adjusted for the same covariates as those in the analysis of gallstone-related acute pancreatitis.

‖One drink was defined as 12 g of alcohol.

¥Physical activity was measured according to minutes of walking or bicycling per day.